MARIHUANA AND HEALTH

Third Annual Report to the U.S. Congress From the Secretary of Health, Education, and Welfare

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THIRD ANNUAL REPORT TO CONGRESS

FROM

THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE

National Institute on Drug Abuse
5600 Fishers Lane
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Dr. Monique Braude -- Sections on toxicity and neurophysiological and endocrinological research in animals.

Miss Eleanor Carroll -- Section on marihuana use in other countries.

Dr. Norman Krasnegor -- Section on behavioral effects in animals.

Dr. Jo Ann Nuite -- Section on pharmacological research in animals.

Dr. Alan Ramsey -- Section on the effects in man, viz: acute physical toxicity, chronic physical effects, genetic and birth defects and psychiatric illness.

Dr. Louise Richards -- Section on extent, patterns and social context of use in the United States.

Dr. Stephen Szara -- Section on the effects in man, viz: the active ingredient, route of administration, metabolism, subjective, physiological and biochemical aspects, intellectual and psychomotor effects.

Dr. Robert Willette -- Section on chemistry and metabolism.

Dr. Robert Petersen edited and coordinated the preparation of the report in addition to preparing the introduction, summary and section on future research directions.

CONTENTS

Acknowledgements	iii
Introduction	1
Summary	3
Extent, Patterns, and Social Context of Use in the United States	21
Marihuana Use in Other Countries	43
Preclinical Research	85
Effects in Man	129
Future Research Directions	161

INTRODUCTION

It is now two years since the first annual report on Marihuana and Health was transmitted to the Congress. During those two years there have been significant advances in our understanding of the implications of marihuana use. Some of these were summarized in last year's report. In addition, a Presidential Commission has carefully considered the marihuana issue and completed its comprehensive examination of many aspects of the problem.

In accordance with the requirements of the "Marihuana and Health Reporting Act" (Title V of P.L. 91-296), the Secretary of Health, Education, and Welfare has the continuing responsibility of submitting annual reports on the health consequences of cannabis use. As in previous years, "health consequences" are defined as the effects of the drug on the individual's mental and physical health, as well as effects of use on the society to the extent that scientific investigation is relevant to that question. Unlike the report of the National Commission on Marihuana and Drug Abuse, however, we have continued to restrict our observations to areas in which a scientific judgment is possible. There are equally important issues of values, law and social custom that have been considered by the Commission and that will undoubtedly be a part of a continuing dialogue within the larger society. By supplying a relatively dispassionate summary of the accumulating scientific data concerned with marihuana and its use, however, it is hoped that this report will be maximally useful to all who are concerned with the present state of our knowledge concerning this socially controversial drug.

A continuing major purpose of these annual reports is to serve as a widely available, up-to-date compendium of scientific information bearing on the issue of marihuana and health. In order to make the report as helpful as possible to the widest possible audience, we have attempted to report findings both technically and, to the extent possible, in more everyday language.

To a greater degree than in previous years, we have placed primary stress on recently accumulated evidence, rather than attempting a more comprehensive overview. More recent research is, of course, evaluated in the context of the total body of our knowledge.

Because it is unwise to overinterpret the uncorroborated findings of any single study, we have again emphasized converging lines of evidence to support many of our observations. Despite more recent evidence, there are still important unresolved questions. One of these concerns the implications of long-term use; another the possible interactive effects of cannabis with other drugs in widespread use. There is significant new evidence regarding the implications of long-term cannabis use. However, much of it is based on overseas populations quite different from an American user population both in their patterns of drug use and in the demands their society makes upon them. Moreover, ours is a society that makes simultaneous use of many drugs. They are used recreationally, as self medication and by prescription. The multiple forms this polydrug use takes makes it especially difficult to be certain how marihuana use may interact with use of these other substances.

Finally, although evidence concerning marihuana use in other cultures remains spotty, the interest in it (and the lack of ready availability of recent information elsewhere) seem to warrant its continued inclusion in the report. Such information has been included only when it updates last year's report.

SUMMARY

In the past year our understanding of the problem of marihuana use and its possible implications has continued to expand at a rapid rate. While some of the advances may appear to the layman to be primarily "technical", all contribute to our greatly enlarged knowledge regarding the health consequences of marihuana use both now and in the future. Much, if not most of the research, is relatively undramatic and its implications frequently are not obvious.

In this summary we will again attempt to translate the findings from many disparate sources into as adequate and complete an answer as can currently be framed to the basic question: What are the health implications of marihuana use for the American people? In attempting to answer this apparently simple, but in reality difficult and complex question, we are well aware that any answers rest on multiple assumptions, many of which are open to question. Present social patterns of typical use may change markedly as may the quality and quantity of the material used. To the extent that marihuana use has some aspects of a fad, we can easily over or underestimate longer term consequences of use. In the past it was frequently suggested that marihuana use might for many supplant alcohol use and thus reduce the severity of the alcohol problem. In reality, it now appears that alcohol use is a typical concomitant of cannabis use. And, of course, with the general increase in marihuana users has also come an increase in those who use it heavily either alone or in combination with other drugs.

As will be discussed in greater detail later, even relatively heavy use in cultures where it is socially sanctioned may have quite different implications from use in a society in which more extensive or even moderate use is viewed as social deviant. Not only are the populations attracted to such use different but so may be the ways in which the user's self concept and ongoing behavior are altered by use. Moreover, in many societies in which use has been largely restricted to the lowest social classes, it is often difficult to know to what extent ascribed characteristics of users represent alterations related to drug use or the institutionalized prejudices of those of higher social status.

We have emphasized in previous reports that any sophisticated understanding of cannabis must take into account many aspects of use patterns. These include such obvious aspects as potency, dosage, and frequency of drug use, but must also include the psychological set and the setting of use, especially the cultural context. When human performance is considered, task complexity, personal values and level of motivation are also important variables.

EXTENT AND NATURE OF MARIHUANA USE IN THE UNITED STATES

Presently available information on the extent and nature of marihuana use is considerably more detailed than it has been in the past. We now have national data concerning use in the general population and relatively detailed studies on youthful use especially among those enrolled in high schools and colleges. There is an accumulating body of data on the social and personal correlates of use and there has been research delineating family and peer relationships of various kinds of users. Information on marihuana and hashish dealers has been included in this report for the first time. The dealer data have been included because dealing and using are frequently carried out by the same individuals, especially if they are regular users.

Generally, the use of cannabis in the United States has not increased dramatically. The rate of increase in some segments of the population may have diminished. Recent estimates indicate that about 24 million persons have ever used cannabis. It should be emphasized that over half of those who have ever used have only experimented with the drug. Probably not more than one in twenty uses on a daily basis. The most common frequency reported by regular users is one to four times per month.

Use is highly age-related and to a lesser extent related to educational status. The highest rates of "ever used" are consistently found among college students (54 percent - an overall increase of twelve percentage points from 1971 figures). Although the National Commission's survey of 1971 found 15 percent of adults over 18 years of age had tried marihuana at some point, other surveys have found lower rates in this group. Since the ways in which data are collected and reported are not consistent across surveys, comparisons are sometimes difficult or can be misleading.

A consistent finding for several years has been that cannabis use is more common in the Northeast and West than in Central or Southern States. It is also more common among urban than among rural residents.

Even though one study found that use by members of military services stationed in the United States (those overseas were not included) was higher than civilians of the same age, additional data are needed to clarify the causes and implications of this finding.

Overall, it has been found that males are twice as likely as females to have tried marihuana. Males are not only more likely to have tried the drug, but are also more likely to be using it with greater frequency. There are, however, many indications that the number of, and rate of use by girls and women is increasing. In college populations, the ratio of male to female use is about 3:2 and recent data on high school use suggest that marihuana use by the two sexes is approaching parity. In several studies the differences in use rates by the two sexes are no longer statistically significant.

Interestingly enough, rates of use are considerably higher in single sex colleges and universities than they are in coeducational institutions. For both

males and females the percentage using tends to be about a third higher in those schools segregated by sex. Social opportunities present in coeducational colleges may serve to reduce overall interest in drug use.

Certain patterns of related drug use have been found. Most characteristic is the use of alcohol and tobacco prior to and concurrently with marihuana use. Among college populations the drugs used, from the most to least frequently, are: beer, wine, hard liquor, lower potency marihuana, higher potency marihuana and hashish followed in diminishing frequency by LSD and other drugs. Heroin use in this group is extremely uncommon.

It has been found that user perceptions of both safety and of availability are significant determinants of choice of drugs although availability is the more important of the two.

A nationwide study of college students' life styles at fifty-four colleges and universities has now done a second year survey of their drug use. During the most current academic year that has been analyzed the percentage of students who have used marihuana during the academic year has risen from 23 to 37. It was found that twice as many students were beginning use as compared to those discontinuing such drug use. The researchers conducting this survey estimate that drug use in the nation's college populations will probably stabilize at about the point where two-thirds make some use of marihuana.

Overall, present trends, especially of frequent or heavy use among high school and college populations, do not appear as alarming as they have in the past. Given some of the fad-like aspects of marihuana use, it can be expected that rates in individual schools will vary widely from the national averages. Judging by trend data in some areas of high use, more frequent marihuana use may be stabilizing and the rate of increase decreasing.

Studies of non-student groups are of particular interest since less is known about them. Health professionals are of special interest because of their sophistication in health matters, their role as models and the possible risk for them associated with drug use. One study of a physician sample in New York City, San Francisco, upstate New York and Nebraska found that over a third of those who responded (about 50 percent of those queried) reported having tried marihuana. Only seven percent reported current use and, as expected, younger physicians and those living in New York City and San Francisco were more frequent users than those in the other areas. Among nurses and nursing students rates of use were appreciably lower. Only three percent of graduate nurses reported ever having used and only a third of these were doing so currently (one percent of total).

Because of the publicity given drug use in Vietnam, military use patterns of marihuana are also of special interest. A worldwide study of enlisted men done in 1971 indicated that somewhat less than a third used marihuana in the preceding year. Not unlike the civilian population, about half would have been more appropriately classified as "experimenters" rather than as users. However, a much higher percentage of users (40 percent) reported using several times per week or more. Use rates, although somewhat higher than for those of comparable age in civilian life, were not strikingly so.

During the past year we have learned more concerning the ways in which people learn about marihuana and the role of family and peer influences in its use. The sources of information most commonly mentioned by children from ages 11 to 17 are television, parents, friends and other students. In the fifth grade reliance seems to be placed on TV and parents. By contrast eleventh graders rate peer influences (friends and other students) as the most important sources.

Several studies have investigated the role of parents and peers in adolescent drug use. The teenagers' use is closely correlated with use by his friends. When none of a teenager's friends reported use of drugs, only one out of fifteen youngsters themselves reported use. When all of their friends reported use, nine out of ten had also used the drug. When brothers or sisters have used, three-quarters of those reporting have also used. Conversely, when their siblings are non-users, half as many giving self reports are themselves users. The more peer-oriented as opposed to parent-oriented the youngster is, the more likely he is to be a user (by peer-oriented is meant the amount of time spent with friends, greater reliance on advice of friends than on that of parents, etc.).

Not too surprisingly, drug use by children is related to drug use by parents. When both parents use drugs such as alcohol, tobacco and other psychoactive drugs, there is a greater likelihood that their children will use marihuana. This relationship has less to do with parents' actual drug use than it does with the adolescent's perception of such use. The probability of drug use is also associated with such factors as lack of family cohesiveness, use of other medications and less parental emphasis on self control.

Marihuana Dealing

The typical marihuana dealer is not a street dealer of such drugs as heroin or cocaine. He is typically himself a user, middle class, not otherwise involved in criminal activity and his selling is closely correlated with his level of use. A user is far more likely to sell if he uses on a daily basis than if he uses only monthly or less often. If he is more heavily involved in the drug culture in that he and his friends are regular users of marihuana and other drugs, he is more likely to deal.

MARIHUANA USE IN OTHER COUNTRIES

There is considerable evidence that cannabis use is increasing among young people throughout the world. Even in those countries in which use has been endemic but previously restricted to the lowest classes an interest in marihuana has developed among middle and upper class youth. This pattern of diffusion seems to have resulted not from emulation of traditional local use, but from adopting the youth norms of Europe and the United States.

Although we have included a brief description of cannabis use abroad in this year's report as we have in the past, we are including additional information only on those countries for which there are new developments to report. It is again worth emphasizing that the uses of cannabis are highly varied. In countries where use is traditional marihuana is more often used as a folk medicine or to make arduous work less so, than it is for recreation. It should be emphasized that the quality of information available on use in other countries ranges from limited, anecdotal accounts to carefully conducted anthropological and sociological research. Unfortunately, the more limited accounts predominate, making comparisons more difficult.

English Speaking Countries

In England, Australia and New Zealand there are indications of an increasing use of cannabis although hard data on the level and patterns of use in those countries are generally lacking. There has been sufficient concern in all three to justify creation of special commissions to look into the problem. The recommendations that have been made by these groups have been generally similar to those made here in the United States - i.e., they have urged a less punitive approach to the user, a more thoughtful examination of the problem, and are supporting much needed research.

In Canada during this past year the Commission of Inquiry into the Non-Medical Use of Drugs published its report on cannabis. The Canadian Commission has functioned very like our own National Commission. It has held extensive public hearings and commissioned a number of studies concerned with Canadian use. Although the data involved have not yet been completely analyzed, Canada has clearly experienced a rapid increase in cannabis use very like our own. From an estimated 79,000 in 1966, the number of those who have used cannabis one or more times has risen to one and a half million. Use appears to be concentrated among young people. The bulk of those who have used are infrequent users and the statistical breakdown and patterns of use appear to be generally similar to those in the United States.

The Canadian Commission's recommendations went beyond those of our National Commission in advocating Federal quality standards for cannabis and permitting sale and distribution subject to restrictions similar to those for alcohol.

Mexico

Although marihuana use has had a long history in Mexico and there has been a recent marked increase in interest in drug problems, there is little in the way of objective surveys to report. While there have been reports of increasing use by middle and upper class youth, there is little evidence to suggest that the increase has been as large as that of our Canadian neighbors.

Other Latin American Countries

Many of the Latin American countries have shown official concern about drug abuse. However, the exact dimensions of the problems are in doubt. In Venezuela, for example, a Special Commission in its report to the Chamber of Deputies indicated that drug use was reaching epidemic proportions. They indicated that some 85 percent of youth in the Caracas area (the capitol) had used drugs at least once. In Ecuador it has been claimed that as many as ten percent of the population are abusing drugs. Although there is some increase in drug use reported in Chile, the very limited amount of data on marihuana use among high school students suggest very few are using (about 7 percent). Generally, these countries are now stressing a multifaceted approach to the problem of abuse including preventive, educational and rehabilitative aspects.

Europe

We have little new information on cannabis use in European countries except for a major survey of student drug use in the Netherlands. Since this study involves three phases, a survey in 1969, one in 1971, and another to take place in 1973, it provides some indication of trends in a country whose drug policy with respect to cannabis has been frequently described as "liberal." In the first survey it was found that 11 percent of the students queried had used an illicit drug one or more times - in almost nine out of ten cases the drug was marihuana or hashish. By 1971 the number had nearly doubled although the percentage of frequent users remained relatively low. The authors of this study are optimistic pointing out that while overall there has been an increase, in schools that earlier had the problem there has not been the expected doubling of rates. Most of the increase can be accounted for by diffusion to new schools rather than a dramatic increase in those already using.

The Middle East

The major source of new data with respect to cannabis use in this area is an extensive study of users in the United Arab Republic. Although there are no exact figures on the number of hashish users, the major researcher concerned with the problem, estimated that in 1967 they comprised about 17 percent of the male population between the ages of 20 and 40. Beginning as early as 1957 an extensive series of studies has been conducted. Data from the most recent study became available this year. Some highlights of this extensive sociological and psychological research include the following: Urban users were found to smoke hashish about fifty percent more frequently than rural users (12 vs. 8 times per month). The ten percent of most frequent users did so 50 or more times per month. Most (62-70 percent) began use before the age of twenty with few doing so after 28. Self described motives for use in order of importance were: group conformity, desire for euphoria, curiosity and the desire to appear like "real men." A small group setting was favored for use of the drug.

The most recent data concerns a prison sample of users matched with nonusers. Among users it was found that heavier users tended to begin earlier and that substantial percentages also used opium and alcohol. By contrast with nonusers, cannabis users were generally found to have fewer criminal offenses and are described as slower learners. Performance on a wide array of psychological testing was generally poorer among users. However, the use of other drugs, the rather heavy hashish use and other cultural factors make the relevance of this data to American use patterns uncertain.

The Far East

New information is primarily available from India and the Philippines. At a recent drug seminar in New Delhi in July 1972, the participants, representing many health and social welfare agencies, agreed that drug abuse is a growing problem among upper class students. Firm statistics to support the extent of the problem are lacking. The delegates emphasized the desirability of launching research studies to determine the extent and causes of youthful drug abuse and the need to encourage more effective prevention efforts by both government agencies and the mass media. A subsequent meeting of the Delhi Medical Association and other health agencies emphasized more effective control over the problem of drug abuse. Efforts to tighten restrictions on the distribution and sale of psychotropic and narcotic drugs are being considered.

Although statistics on the extent of marihuana abuse in the Philippines are also limited, it has been estimated that 60,000 youths are engaged in drug experimentation, mostly with cannabis. As a result of an increasing concern with many aspects of drug abuse over the past several years, a number of new organizations and facilities have been created and new legislation has been passed. The new law creates a Board with broad responsibilities for developing educational programs, special training of police and rehabilitation personnel and conducting drug research.

Jamaica

A major study of thirty lower class users matched with an equal number of nonusers was completed during the period covered by this Report. In addition to the biomedical research commented on elsewhere, a systematic effort was made to understand the context of use on the island. Users are predominantly from the lower class and marihuana, called "Ganja" in Jamaica is used for many purposes. It is smoked, chewed, taken in tea, cooked and added to food. It is widely used as a folk medicine as well as to ward off fatigue or to help endure discomfort. It is estimated that two out of five adult males are regular users who typically smoke the drug as a work adjunct. Although it is widely believed to facilitate work performance and increase energy output, careful research conducted by anthropologists using videotape recordings did not support this belief.

Cultural expectations with respect to marihuana bear little resemblance to American and European views of the drug which emphasize the recreational,

"mind expanding" aspects. Rather it is seen as an aid to more alert work functioning. Although the age of introduction appears to be declining, use is typically begun in the early teens and represents in part a rite of passage into manhood.

Most recently, as in other parts of the world, there has been increasing concern expressed regarding the diffusion of use to include middle and upper class youth. This use, like that of the lower class, is illegal, but unlike the use by the working class, is not generally sanctioned by members of the group.

PRECLINICAL RESEARCH IN ANIMALS

Animal research continues to be an important source of increased knowledge about the implications of cannabis use by humans. The genetic history of animals can be controlled as can their learning history, their drug use and the environmental conditions surrounding them. This makes it possible to study problems which, for ethical, scientific or practical reasons, cannot be studied nearly as well in humans. At the same time it must be kept in mind that animal-human differences in physiology, the greater complexity of the human situation, differences in dosage levels and the possible role of multiple drugs in real life human drug use, all make difficult the direct translation of animal results into human terms.

Perhaps the most important finding deriving from animal research in the past year is that both synthetic Delta-9-Tetrahydrocannabinol* and natural marihuana, even when given in relatively high doses over extended periods, apparently have no deleterious effects on pregnancy, fetal development or the newborn. Testing was done in accordance with the guidelines of the Food and Drug Administration for assessing possible adverse effects of drugs on pregnancy and fetal development. Although this finding is reassuring, it illustrates some of the problems alluded to above. There is no way of being certain that cannabis when used in combination with other drugs might not produce adverse effects that may not occur when used alone. Although there is, at present, no evidence of this, even the remote possibility makes it desirable that unnecessary drugs including cannabis not be used during pregnancy.

Although our knowledge has expanded of the ways in which marihuana and Delta-9-Tetrahydrocannabinol are rapidly changed into their metabolites, the specific role of each is still not certain. Several of these metabolites appear to be psychologically active.

One of the more interesting effects of Delta-9-Tetrahydrocannabinol in animals is that it increases the depressant effects of barbiturates and yet it also

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* In order to simplify the text, when THC is used without qualification it refers to Delta-9-Tetrahydrocannabinol - the presumed principal psychoactive material in natural material.

enhances the stimulating effects of amphetamines. The clinical implications of this finding in the human use situation are not yet clear although it may be a factor in multiple drug use.

The issue of tolerance was discussed in some detail in last year's report. According to recent studies it appears certain that tolerance develops, at least at high doses in animals, for some of the effects of cannabis. This marked tolerance, however, has not been adequately reproduced in man. The ways in which tolerance may be complicated by drug interactions is illustrated by animal research which suggests that rats which have developed tolerance to Delta-9-Tetrahydrocannabinol are in turn less susceptible to the acute effects of alcohol. Conversely, rats tolerant to the effects of alcohol appear to be less affected by Delta-9-Tetrahydrocannabinol. While this question has not been systematically investigated in man, it suggests that heavy users of alcohol may have greater resistance to the effects of marihuana and vice versa. The basis for this apparent cross tolerance is not known at the present time.

Although an abstinence syndrome following prolonged administration of Delta-9-Tetrahydrocannabinol has been found to occur in Rhesus monkeys, this result must be interpreted with caution. The syndrome, consisting of hyperirritability, increased aggressiveness, muscle tremors and yawning, has thus far only been found in a small number of animals under heavy dosage conditions.

An early Russian report of a specific antagonist (phenitrone) to the action of marihuana, i.e., a drug which blocks its actions, has not been substantiated by other investigators. However, evidence that cannabidiol, a natural ingredient in marihuana, may prevent the depressant effect of Delta-9-Tetrahydrocannabinol in mice, is resulting in an increased interest in the possibility. It also suggests that the action of the natural material is complex in that additional ingredients other than Delta-9-Tetrahydrocannabinol may modify the effects.

At present, the relationship of marihuana use to various aspects of brain chemistry is still under study. However, early results have shown that marihuana has specific effects on neurohormonal distribution, i.e., on the compounds which are involved in the mechanism of action of most psychoactive drugs.

A variety of attempts to examine the possible effects of cannabis and Delta-9-Tetrahydrocannabinol on lung function are currently underway. In one study of isolated lung tissue, smoke from marihuana cigarettes was found to cause changes in cells similar to changes caused by smoke from ordinary tobacco cigarettes. This suggests the possibility that marihuana may be a lung irritant like tobacco. The implications of this for an American population are uncertain since despite deep inhalation the frequency of typical American use of marihuana is so much lower than that of tobacco.

Studies of animal behavior while under the influence of marihuana and Delta-9-Tetrahydrocannabinol are of particular interest because of the high degree of control that can be exerted over learning history and other variables affecting behavior. Two areas that are of special interest are the effects on time

perception and on aggression. There is objective confirmation from the animal laboratory that time perception is altered in animals in ways similar to those reported by human users. There is also evidence that marihuana and Delta-9-Tetrahydrocannabinol generally reduce aggression in animals. However under chronic administration, the opposite effect occurs in animals, i.e., cannabinoids produce hyperirritability and increased aggressiveness. Further exploration of conditions under which this is true may help to better understand marihuana's effects on aggressive behavior in humans. There have been some anecdotal accounts of marihuana-related aggression in humans although the predominant view is that it tends to induce greater passivity. Animal research may help to explain the somewhat contradictory reports stemming from different levels of intoxication, extent of use and possible abstinence effects.

EFFECTS IN MAN

Although many of the immediate effects of marihuana were described in last year's Report, the past year has provided additional verification of some of these observations and clarification of still others.

While it is now rather firmly established that Delta-9-THC is the principal psychoactive ingredient, other chemically identified ingredients of the natural material play a role in producing some of cannabis' effects. Delta-8-THC, a related compound to Delta-9-THC which occurs in relatively small quantities in the natural product, has been found to be psychoactive, although somewhat weaker than Delta-9-THC. Cannabadiol, another natural ingredient, has been found to produce slight changes in subjective feelings and an increased pulse rate. Since, in at least one animal study, this ingredient has been found to block certain effects of THC, it is possible that its presence in natural material modifies the response to THC in man as well. However, there is no indication at present that Delta-9-THC is not capable of reproducing the total subjective and objective effects of the plant material.

Marihuana and THC are physiologically transformed in the body into metabolites such as 11-Hydroxy-Delta-9-THC. A number of these metabolites have now been positively identified and are being carefully studied. A simple method of detecting cannabis smokers by having them breathe on chemically treated paper has been suggested. Although the method is sensitive for two hours after use, the smoking of tobacco interferes with results and the test is not yet practical.

The role of user expectations in perceived marihuana effects has been underscored by research in which inactive material (placebo) was subjectively seen as having generally similar effects to those of marihuana. These effects were, however, described as only a third as intense as those with the active drug. Particularly at lower doses, the role of expectations and the setting of use help to explain the wide variations of subjective response that would not be readily predictable from the drug's pharmacologic profile.

Immediate physiological effects such as increased pulse rate, reddening of the eyes and a decrease in intraocular pressure reported last year have been

systematically investigated. There is some concern that a persistently high pulse rate produced at the time of marihuana intoxication might be dangerously increased by the use of certain other drugs in treatment following say, an auto accident. There have, however, been no reports of serious consequences ensuing.

A careful study using thirty young male volunteers indicates there is little question that marihuana reduces intraocular pressure in a dose-related way (i.e., the higher the dose the greater the pressure reduction within the eye). THC appears to be the ingredient in cannabis primarily responsible for this effect. The obvious potential of this effect for the treatment of glaucoma, an eye disease in which increasing intraocular pressure can impair vision, has been investigated on a very limited basis. However, before cannabis or THC can be used routinely for this purpose, considerable further study and testing are required. Its superiority over drugs presently available for this purpose remains to be demonstrated.

A number of studies concerned with more subtle physiological effects of cannabis have been conducted. The effects of marihuana on breathing are being studied as are its effects on electrical activity in the brain and on sleep. The results of most of this research are primarily of technical interest at this time. One interesting aspect of the sleep research is that marihuana, which was expected to enhance dreaming, did not do so.

In studies done on the vestibular system (a system in the inner ear essential to maintaining proper balance) the effect of marihuana in social dose levels has been found to be negligible in one study and in another to interfere with balance only with closed eyes at higher dose levels.

With respect to psychomotor and intellectual functioning, a consistent finding has been that the more complex the task demands, the more consistently they are affected by marihuana intoxication. As has been pointed out in the past, more experienced users seem to be, in general, better able to compensate for the drug effects than are the inexperienced.

Driver Performance

In previous years the limited data on driver performance cast doubt on whether marihuana use at the usual social levels seriously impaired driver performance. At the present time there seems to be little question that marihuana use impairs performance. In one study poorer automobile handling performance was found with both alcohol and marihuana although driving speed under marihuana was consistently slower. In another study it was found that marihuana resulted in longer reaction times and a greater frequency of wrong and inadequate driver responses to a simulated driving task. In a simulated automobile passing task both alcohol and marihuana affected decision-reaction times although alcohol did so to a greater extent.

In a set of experiments designed to study the effects of alcohol and marihuana on driving-related visual functions, it was found that marihuana interfered

with peripheral vision as well as central vision to a greater extent than alcohol under a wider variety of task demands. This deficit was interpreted as the result of momentary lapses of attention under marihuana intoxication. Apparent movement of a fixed light source which might also be important under some driving conditions was only insignificantly changed by alcohol but more markedly affected by doses of cannabis within the usual social range. Contrary to a preliminary report included last year, there was no evidence of an impairment in glare recovery time (the time required to readapt following exposure to such glare as oncoming headlights) associated with marihuana use.

In another study marihuana was found to interfere more than alcohol with performance when subjects had to time their response accurately in order to respond correctly. Even when subjects received an immediate indication as to whether their responses were correct, early or late, those under the influence of marihuana in contrast with alcohol, made a greater number of errors.

Although additional research on cannabis, driving and driving-related tasks will be helpful in better understanding the mechanisms by which driver performance is impaired, there is sufficient evidence at this time to justify the warning that even social doses of marihuana may impair performance sufficiently to lead to motor vehicle accidents. Systematic research on the effects of marihuana in combination with alcohol and other drugs on driving has not yet been undertaken. It is, however, reasonable to expect that combinations will often be more hazardous than marihuana used alone.

Chronic Physical Effects

While there is little evidence to suggest that there are deleterious physical effects arising from a single episode of use or from infrequent use of marihuana, the issue of long-term, chronic use and its effects remains unresolved. It is generally conceded that there is no such thing as an entirely "safe" drug and cannabis is not likely to be an exception. As has been pointed out in previous Reports, most of the earlier accounts of chronic effects are by current scientific standards seriously deficient. Current clinical case reports dealing with one or more cases may provide clues for more systematic study but rarely in themselves prove a causal connection between drug use and its presumed consequences. While there have been more systematic studies of users matched with nonusers these too can be faulted on a variety of grounds. If the adverse consequence of chronic use is rare or very subtle it may go undetected especially when small numbers of users are studied. Again, as has been suggested in earlier reports, when several sources of data - the laboratory, clinical observation, animal and human research - converge toward a common conclusion, we can be more confident of its validity. In this Report as in the previous versions we have attempted to report even on single case studies of interest. This is done to suggest where more systematic observation is needed as well as to give some indication of the present state of our knowledge.

Among the case reports that have appeared in the past year is one indicating breast enlargement in three young adult males with a history of several years

of relatively heavy marihuana use. In the absence of other causes (e.g., liver or glandular abnormality) the authors speculate that the similarity of the THC in marihuana to a hormone having a feminizing effect may be the cause. Although there have been some reports of liver abnormalities associated with cannabis use, more systematic studies of larger samples have not confirmed this. It is noteworthy that in a study of chronic users in Jamaica carefully matched with nonusers and conducted under NIMH aegis, no evidence of liver damage was found nor was such evidence found in a Canadian study of 200 regular cannabis users.

Since the Jamaican study represents a significant attempt to study all aspects of possible effects in chronic users under carefully controlled circumstances, it is described in some detail in the body of the Report. In all, sixty carefully matched male users and nonusers from a lower class Jamaican population were studied. These men averaged thirty-four years of age and had typically been smoking relatively strong marihuana for over seventeen years at the rate of seven cigarettes per day. They were subjected to very thorough physical and psychiatric examinations including measures of psychological and neurological functioning. Results of this study have integrated into the appropriate sections of the Report.

A relatively consistent observation even from the earlier scientific and medical literature has been that chronic users experience respiratory problems. In the past year additional reports have appeared that support this observation. A report based on 200 cases of heavy hashish smokers stationed with the U.S. Army in Europe emphasized a variety of upper and lower respiratory complaints. While most of these were relatively minor, ten percent of the group had bronchitis and showed diminished lung capacity (vital capacity). Microscopic examination of bronchial tissue in this subsample showed abnormal changes described as similar to those found in older, heavy cigarette smokers. A study of seventeen additional heavy hashish users from the same source further confirmed this observation.

While there were no important statistically significant differences between users and nonusers in the Jamaican study, there was a tendency for various lung functions to be diminished with increasing years and total quantity of use. It should be emphasized that this relationship appeared to be more closely related to any type of cigarette smoking (tobacco or marihuana) than to marihuana use as such.

As has been noted earlier, there is also some evidence that isolated lung tissue exposed to marihuana smoke shows greater cell changes than that exposed to cigarette smoke. A number of additional studies are being conducted to further explore this important question.

The issue of possible brain damage was highlighted early in the year by a report on thirteen young adults referred for psychiatric treatment. The authors' clinical impression was that the symptoms shown (apathy, mental sluggishness, loss of interest in personal appearance, recent memory problems, mental confusion, etc.) were related to the level of marihuana use and its toxic effects on the brain. Some of the symptoms described are like those of

acute marihuana intoxication and in view of the inherent sampling bias (the patients were referred for their difficulties rather than randomly chosen from a population of users; they had also used other drugs), it is difficult to be certain of the role that cannabis played. Since there is no simple test of cannabis intoxication, it is possible that some of the patients were actually using the drug shortly before examination. In the Jamaican study there was no evidence of brain damage in the sample studied.

Twenty-three heavy hashish users referred as part of a much larger group of American soldiers having psychiatric complications related to hashish use continued to show confusion, memory loss and inability to concentrate after they discontinued hashish use. The authors view these symptoms as consistent with brain damage, but since there was no objective way of confirming that cannabis was no longer being used or the extent of other drug use, interpretation is difficult.

Details of an extensive study of 850 hashish users in the United Arab Republic became available this year. These users and a population of nonusers, both drawn from prison populations were given a variety of tests of psychomotor and intellectual performance. While users had lower scores than did nonusers, interpretation is complicated by the fact that users had also frequently been users of opium as well. Despite the relatively large number studied, the lack of additional detail (e.g., on nutrition and other aspects of life style) limits any conclusions that can be drawn.

Systematic study of brain electrical activity (EEG records) in matched user-nonuser populations in both Jamaica and Greece have not disclosed abnormalities associated with cannabis use.

Based on present evidence it is not possible to offer definitive conclusions regarding a possible association between heavy cannabis use and organic brain damage. The obvious seriousness of such a consequence, particularly if it is irreversible, continues to make research on this question a high priority issue.

Genetic and Birth Defects

The possibility that cannabis preparations might cause genetic or birth defects has been a source of concern although there has been little evidence to support it. The bulk of present evidence, particularly that of well controlled studies, suggests that the likelihood of genetic or neonatal abnormalities arising from cannabis use at present social levels of use is low. There is no convincing evidence that chromosomal abnormalities arise from marihuana use. The Jamaican study of chronic users as well as other studies of the effects of THC on chromosomes in human lymphocytes (a type of white blood cell) indicate no changes related to cannabis use. Although there have been isolated case reports of abnormal offspring born to mothers who have used marihuana and other illicit drugs during pregnancy, more systematic controlled investigation has not borne this out. As has been indicated, animal research at substantially higher dosage levels than those likely to be employed by users showed no evidence of hazard to fetal development.

Despite this lack of evidence of hazard it should again be emphasized that there is no way of being certain that cannabis, possible in combination with other drugs, might not have adverse reproductive consequences under some circumstances. The potential seriousness of such effects makes the use of marihuana during pregnancy particularly unwise.

Cannabis and Psychopathology

The relationship between cannabis use and possible psychiatric disorders arising from its use has been of interest for many years. Unfortunately, virtually all of the earlier studies dealing with this issue have suffered from multiple deficiencies. Since previous reports have described their defects in some detail, we will only reiterate that they have suffered from such shortcomings as: Biased sampling, poor diagnosis, failure to distinguish preexisting psychopathology from that related to use, other confounding variables, etc.

During the past year a number of reports have appeared relating to psychiatric problems associated with cannabis use. In one military population (U.S. Army personnel stationed in West Germany) two percent were referred for medical reasons related to hashish use. Sixty percent of these were infrequent users with minor respiratory problems related to use. A small percentage of the group referred (less than three percent) had acute panic reactions or toxic psychoses related to a single high dose of hashish. The remainder showed symptoms ranging from acute psychosis (related to hashish and other drug use in combination), to chronic cannabis intoxication of a degree that interfered with functioning. While infrequent lighter use had few psychiatric complications, heavy use and use in association with other drugs had a variety of adverse effects. A Scandinavian study of acute and chronic psychoses associated with cannabis use (mostly of hashish) found that most of those with a chronic psychosis had had a previous history of serious mental illness. By contrast, less than ten percent of those who had had acute cannabis-related psychoses lasting from one to five weeks had such a history. Typically there had been a marked increase in cannabis use just prior to the episode.

Several American studies have suggested that frequent users are more likely to admit to psychological distress than are nonusers or to have verified psychiatric problems. Evidence cited in previous Reports suggests that this is especially true of heavy users.

Whether or not cannabis is a causal factor in an "amotivational syndrome" is still an open question. While a loss of conventional values with their stress on competitive career achievement has been commented on by numerous observers, it is often difficult to separate a possible drug-use related loss of motivation from that produced by the prevailing values of a youthful counterculture. Thus, it is difficult to know whether the value shift resulted in greater emphasis on drug use or vice-versa. While a decline in conventional motivation has been attributed to cannabis use in other cultures, evidence from the Jamaican study does not suggest that chronic users are less motivated than nonusers. Present studies of longer term users and of drug user careers in

the United States may be helpful in clarifying this issue.

Overall then, present evidence suggests that marihuana use can result in psychiatric complications under some circumstances. Such complications, including acute panic and psychotic reactions, appear to be more common in those with a previous history of psychological difficulties or in those taking larger doses to which they are not accustomed. Nevertheless, serious complications of cannabis use appear to be relatively infrequent. Chronic cannabis intoxication can be a problem in much the same way that chronic alcoholism is although there is little basis for knowing the comparative risk each of the drugs might pose under conditions of equal social acceptability. Loss of motivation resulting from cannabis use remains an unverified possibility although there is little to suggest that it is an inevitable consequence of chronic use.

FUTURE RESEARCH DIRECTIONS

Our knowledge of the health implications of marihuana use has rapidly expanded over the past several years. However, there continue to be important areas in which additional research is needed. One of the most important is an expansion of research both here and overseas on the implications of chronic use. In addition to making us aware of the health implications of widespread use such research can provide insight into the cultural context of use that may be helpful in limiting possible adverse effects.

Other important areas for expanded research include: Study of marihuana use patterns among various segments of the population including minority groups, longitudinal studies of users over extended periods to determine the relationship of drug use to other aspects of life style, studies of the role of peer, family and institutional influences on patterns of drug diffusion, development of uniform data collection procedures, development of more sophisticated epidemiological methods and cross cultural studies of cannabis use. Research in these areas will better enable us to estimate the degree of public health problem that marihuana use is likely to assume in future years and may provide valuable clues to methods of minimizing the public health hazard.

There is a continuing need to probe the implications of marihuana use in industry and the possible hazard to industrial safety which such use may entail.

Study of the biomedical aspects of marihuana use remains an essential ingredient of a continued program. The study of larger samples of chronic users abroad so as to detect less frequent hazards of long-term use is an essential aspect of this activity. Further knowledge of the mechanisms of action of marihuana and of the way in which it is physiologically transformed in the body are important areas. Such research can enhance our understanding of marihuana itself, and may help us to anticipate possible adverse consequences of the interaction of marihuana with other commonly used drugs.

Attempts are currently underway to develop uniform analytical methods in order to insure that analyses of cannabis here and abroad are comparable. Another

important technical goal is that of developing a simple, easily applied test of the level of marihuana intoxication. Such a test will be invaluable for both clinical and research purposes.

The study of the interaction of marihuana with a limited number of other drugs, including alcohol, is already underway. This work needs to be systematically expanded in order to better assess health hazards that may be posed by multiple drug use.

Possible adverse effects on specific organ systems such as the heart, lungs and central nervous system must be systematically studied both in animals and man.

There have been a variety of clinical reports of various symptoms which may be related to marihuana use. These and other clinical case reports must be carefully followed up by well designed animal and human research to determine the role of marihuana and other possible causative factors. It might be possible, for example, to develop an animal model for the frequently reported "amotivational syndrome" to examine cannabis effects which would be difficult to study in human populations.

EXTENT, PATTERNS, AND SOCIAL CONTEXT OF USE IN THE UNITED STATES

This section contains a summary of present use patterns and trends in the 1972 report. Brief summaries of the conclusions of that report are given, followed by new data available since its preparation in late 1971. There are two parts of this section that treat new topics in more depth than in former reports, however. These are concerned with sex differences in use, and drug selling. Research results that were omitted from previous reports and that seem particularly relevant today are also included.

There is an increasingly solid mass of data on which to base descriptions of marihuana use in late 1972, compared with that which was available for the Marihuana and Health Reports of 1971 and 1972. The full report of the National Commission on Marihuana and Drug was released shortly after the 1972 report and included results of a detailed nationwide survey of marihuana use. (27) New figures are also available from the National Commission representing overall rates for 1972. (35b) Several surveys included in the past two Marihuana and Health Reports have new data to report comparing past with present rates. (5,32,37) An updated cumulative list of studies, surveys, and polls of illegal drug use of all types has also recently been published. (4) Significant studies of special subjects such as family and peer influences, personality, and drug dealing have been reported during the past year. (7,8,20,18,34) Thus a more adequate picture of the epidemiology and etiology of marihuana use is now possible.

Despite these advances, there are certain questions still unanswered. Among these are questions about the nature of the spread of use, the nature and conditions of cessation, the role of the law, and attitudes and communication influencing use. In addition, patterns of marihuana use in older age groups are less known; the same is true of use patterns among ethnic minorities at all ages.

The issues of confidentiality and validity of data are still a concern in research on marihuana use. Most researchers make a special effort to protect the anonymity of subjects. This is both to protect the subjects from inadvertent disclosure of their illegal behavior and to improve the chances that their self-reports will be accurate. There is evidence that falsification of high school students' self-reports is low, probably under five percent of a given group. (10) Several years have passed since many surveys and polls were initiated, and the continuing lack of evidence of large discrepancies gives us some measure of confidence in these data.

Unfortunately, the methods of measurement of marihuana use, as well as that of other illicit drug use, are not consistent across studies. This makes it somewhat difficult to compare results. Consistent treatment of frequency, regularity, and recency of use, as well as the differentiation of marihuana and hashish, are not found as often as would be desirable.

ESTIMATES OF RATES OF NATIONWIDE CANNABIS USE AND CHANGES IN 1972

The 1972 Marihuana and Health Report described two major sources of estimates of marihuana use in the general population. McGlothlin provided an estimate that by mid-1971 nine percent of the total population age 11 and older had used marihuana at some time. (26) Within the group of users, he estimated that almost half (46 percent) had stopped using or had used less than ten times. Only three percent were using daily, and the rest were using less than daily but at least once a month. Data collected in a nationwide survey by the National Commission on Marihuana and Drug Abuse released in January 1972 indicated higher rates: 14 percent of 12-17 year olds and 15 percent of adults 18 years and older, for an estimated total of 24 million persons. (27) Three types of users were portrayed. The range of percentages of each was: experimenters 50-60 percent; intermittent users 2-19 percent; moderate users 5-6 percent; and heavy users 2-4 percent.* At the time of the 1972 report, the discrepancy between the two nationwide estimates could not be explained except possibly as the result of different methods used in the surveying or estimating procedures.

One year later, in mid-1972, McGlothlin again estimated total nationwide use for persons 11 years and older using all available survey data. (23) The overall percentage who had ever used was estimated as 14.2 percent, a total of slightly over 22 million persons. The distribution by age or grade and sex was:

Percent Who Ever Used Marihuana, Mid-1972[a]

	Mid-1972		
	Total	Male	Female
Grades 6-8	7	8	6
Grades 9-12	28	32	25
College	54	62	41
Age 18-24 (nonstudent)	30	39	20
Age 25-34 (nonstudent)	15	19	10
Age 35+ (nonstudent)	6	9	3
Total, age 11 and over	14.2	18.9	9.5

a McGlothlin, 1972

The National Commission on Marihuana and Drug Abuse estimates of the rates for the total population for mid-1972 are close. The estimate for the 12-17 year group is 14 percent and for the 18-and-older group, 16 percent. (35b) McGlothlin's estimates are well within the tolerance of sampling error of the Commission's study. Thus, the proportion of the population of 11 years and older who have ever used marihuana lies between 14 and 16 percent.

* These percents did not total 100 percent because a small proportion of respondents did not answer the question.

According to McGlothlin's estimates for 1971 and 1972, total marihuana use increased about 5 percentage points during the year (from 9 percent to 14 percent). The Commission's two studies, however, indicate a much smaller increase - 1 percentage point at most. There is no satisfactory resolution of these differences, since inexactness exists in either set of estimates. Evidence from repeated surveys of segments of the population indicate, however, that stabilization of rates probably is occurring among adolescents.

McGlothlin estimated that hashish use was about 20 percent of total marihuana use in mid-1972 and that it had increased. (23)

There is some tentative evidence that rates of exposure to marihuana may be stabilizing for the teenage group. Results of a nationwide household interview survey of youngsters 12 to 17 years old conducted in May 1972 have now become available. (37) They show that the 15 percent rate found in an earlier 1971 survey did not change; the same proportion was found in 1972. A West Coast junior and senior high school survey that has been repeated consecutively for four years also reports virtually no overall increase in marihuana use. (5) Details of these findings are described in the section on Marihuana Use by Students below.

In McGlothlin's mid-1972 estimates of frequency of use, about the same proportion as in 1971 had stopped using or used less than 10 times (48 percent); a few more were using daily (5 percent); the rest were using at intermediate frequencies (20 percent at 1-4 times a month, 17 percent at 1-2 times a week, 10 percent at 3-6 times a week). The differences between these figures and those from 1971 are so slight as to be virtually non-significant. The National Commission's detailed findings of this type will be available in their 1973 report.

A consistent finding has been that states in the Northeast and West have considerably higher rates of use than those in the North Central area or in the South. Residents of metropolitan areas used marihuana more often than rural residents. Use has been found to be slightly higher among persons with above-average incomes and distinctly higher among those with higher education. Rates did not differ significantly among racial groups and only slightly by religious affiliations. (26) There is no new data suggesting that these patterns have changed.

Youth continues to be a strong correlate of marihuana use, though the over-25 groups have experienced an increase in use, according to McGlothlin's estimates. College students nationwide have used marihuana at a considerably higher rate than their non-college counterparts. (23) A nationwide study of high school graduates one year after graduation highlights aspects of this transition point with regard to drug use. (1) In 1970, non-student youth during their first year out of school used at the same rate as college freshmen. (This rate rose from 21 percent of the high school seniors in 1969 to 34 percent of the same group in 1970.) In 1969, the college bound seniors had had a somewhat lower rate than the non-college bound in the first year of the study, but in 1970 were "catching up" in the freshmen year. Based on estimates

of college student use shown above, use rates of college students continue to increase at a rapid rate in subsequent years.

There is comparatively little data regarding the kinds of persons most apt to adopt marihuana use when they are no longer students. The study mentioned above offers an interesting finding, however. (1) It found that males with the highest rate of "conversion" to drugs (including marihuana) one year after high school were those in (domestic) military service. (Those in overseas military service were not included in the study.) The group with the lowest rate were employed in civilian jobs. There are several implications in this finding, but more data need to be collected on a longitudinal basis for firm conclusions to be made.

Findings are fairly consistent across studies regarding one related behavior of people who have ever used marihuana. They are more apt than nonusers to make use of such legal drugs as alcohol and tobacco. This finding has appeared repeatedly in studies of students and also was found in the Commission's survey results on adults. (27) Differences in frequency and regularity of use must be taken into account in identifying "types" of users. As use spreads to broader segments of the population it is to be expected that users will more and more resemble the "average person."

Sex Differences

McGlothlin, summarizing marihuana use rates in student populations for 1972, states, "For college students, the male-female ratio is about 3:2, and is somewhat closer at the high school level." (23) His data also indicated that in the general population, males were about twice as likely to have tried marihuana as were females. Not only have more males than females tried marihuana, males are also more likely to use the drug with greater frequency. The proportion of females who have used marihuana three or more times per week is about half that for males. Recent data indicate, however, that there is a trend toward increasing use of marihuana among females.

One study based on an area of relatively high use reports that the number of females who have used marihuana has increased since 1971. (5) In the category of "any use during the year," male and female rates for grades 7 through 12 were strikingly similar. Males tend to average a few percentage points higher than girls, but the overall differences are slight. The percentage of marihuana use was found to be from 17 to 61 percent for males and from 13 to 53 percent for females, depending on school grade. Both male and female rates increased slightly after 1971, but the difference in use between the sexes is not great. The details of those differences are seen below:

Marihuana Use in San Mateo Schools, by Sex and Frequency of Use, 1971 and 1972[a]

	Any use in the past year		10 times or more		50 times or more	
MALES						
GRADE	1971	1972	1971	1972	1971	1972
7	17.6	17.2	5.3	5.8	-	-
8	29.1	33.3	14.6	17.2	-	-
9	44.4	43.9	26.1	26.8	17.2	15.9
10	49.7	51.9	33.3	36.8	23.2	25.5
11	57.9	58.0	42.3	41.2	30.2	28.2
12	59.1	60.8	43.7	45.0	32.3	31.7
FEMALES						
7	12.6	13.2	4.1	4.6	b	b
8	25.8	29.2	12.4	14.1	b	b
9	40.5	39.0	23.3	23.0	11.6	12.5
10	48.1	49.3	31.1	32.2	17.0	19.1
11	49.6	52.4	32.6	35.7	19.3	20.7
12	48.3	53.0	30.6	35.5	18.5	20.4

a Blackford, 1972
b Information not available

The San Mateo figures are consistent for "use ten times or more" and "use fifty times or more." Again, males tend to average only about five points higher than the females for each category. The range for "10 times or more" was from 6 to 45 percent for males, and from 5 to 36 percent for females. For the "50 times or more" category, rates ranged from 16 to 32 percent for males and 13 to 21 percent for females. (5)

In another recent study conducted in Montgomery County, Maryland (a Washington, D.C. suburb), also on junior and senior high school students, both males and females showed significant increases in marihuana use over 1969. However, the differences between males and females' use were not pronounced. The reported rates for those who had used marihuana, but had ceased, were from 2 to 20 percent for males and from 2 to 15 percent for females. However, rates of daily use for males appear to be almost twice as high as those for females. An exception was found in the tenth grade where the rate for females was slightly higher than that for males (males: 4.2 percent; females: 4.8 percent). By the senior year, the daily usage rate for males was more than twice that of females (males: 7 percent; females: 4 percent). (11)

In the Montgomery County study, the monthly and weekly rates varied with age (or grade level). In some instances, the males' rates were higher, in others it was the females'. The data indicate that at either extreme (7th or 12th grade), the males' usage rate exceeds the females', although there may be variability in the middle grades, with the females' rates often exceeding the males'. (11)

Similar results were also obtained from a study of current users of non-medical drugs at one university. Data from a four-year period show that the rates for male usage of marihuana and hashish was 95 percent, and for females, 91 percent. (9)

In many instances male-female differences do occur as expected. A study conducted in North Carolina on forty-four junior and senior high schools, for example, showed that 29 percent of the males and 20 percent of the females reported trying marihuana at least once. (24) It might be expected to follow this traditional pattern in the South and other areas where marihuana use has not been as heavy as in coastal and urban areas.

In one interesting analysis of institutional differences in marihuana use, coeducational institutions were compared with all-male and all-female schools. (14) The rates of marihuana use were generally lower at the coeducational institutions. The findings from this study indicated that drug usage for both males and females at co-ed schools is not as great for either sex as it is at single sex institutions. It appeared as though the presence of members of the opposite sex on campuses lowered the amount of marihuana use for both males and females. The reported rate for males at all-male institutions was decidedly greater (58 percent) than their rate at coeducational institutions (41 percent). This difference was also reported for the female colleges (31 percent) versus 25 percent in co-ed schools. The overall rate for both males and females was 34 percent at coeducational schools, less than the combined rates for males and females at single sex colleges and universities. The

study concludes, "...heterosexual relations may well play an important role... in reducing drug participation." (14)

These studies shed more light on the question of male-female differences in drug use. Generally, the studies indicate that there is not as great a difference between male and female use of marihuana as has existed in previous years. However, with larger amounts of marihuana and increased frequency of use, the males' usage rate still remains somewhat greater than the females'.

MARIHUANA AND INDIVIDUAL DRUG HISTORIES

There is very little new data to report on individual marihuana use patterns over time. As noted above, on a nationwide basis, about half of all those who ever used marihuana are current users. Half are virtual nonusers, having used it less than ten times. (23) In the nationwide study of teenagers in 1971, however, it was noted that the size of the group who continued use beyond initial experimentation was larger for marihuana use than for any other drug. (10)

It is important to keep these aspects of use clearly in mind when assessing the extent of marihuana use. Different conclusions can be drawn depending on the type of question asked, as was pointed out by researchers studying students' drug use in New Haven over a two-year period. (3) Increases in those who "ever used" were highly evident, but when "currently use" was recorded separately, the increases were much less evident for most drugs. In the case of marihuana, current use did increase slightly from 1971 to 1972, but it was not as pronounced as the increase in "ever used." The latter group, of course, include many teenagers who have experimented only once or twice.

Studies of the duration of use, in contrast to frequency or regularity of use are few. Some longitudinal studies are attempting to trace individual use patterns over time, but none has been in operation long enough to make conclusive statements about typical use histories. Since many users are in younger age groups, it will be a number of years before adequate long-term drug histories from these groups are available. One study of hippies followed up after their initial visit to the Haight-Ashbury Clinic (beginning in 1967) suggests a pattern that might be expected of multiple drug users from that unique subculture. (36) Based on data from those who could be located and interviewed several years after contact with the clinic, it appears that the use of a wide variety of drugs has declined but that a majority of this group continues to use marihuana and the milder psychedelics.

Associations between marihuana use and the use of other drugs are similar to those previously reported. The pattern of association between alcohol or tobacco use and that of marihuana has been mentioned. If other drugs are used, marihuana is typically the first illegal one in the sequence. Users who associate with "hard" drug users and are involved with selling are more likely to later use opiates and cocaine. (16, 17)

Several interesting conclusions were drawn by investigators testing the incidence and frequency of use of a number of illegal drugs for underlying consistency. The investigators were interested in whether the adoption of various drug use follows a predictable pattern of mild to strong, and in learning any other basis for decisions to use or not to use a particular drug frequently. (33)

They found that among college students a predictable pattern does occur. The various drugs tried can be predicted reliably from knowledge of the last one tried. The substances could be ordered as follows from greatest to least extent of use: "Beer, wine, hard liquor, midwestern pot, non-midwestern pot, hash, LSD, mescaline, speed, barbiturates, opium, psilocybin, THC, MDA, thorazine, cocaine, DMT, and heroin." (This pattern held true for another sample of drug users, but not for an ex-addict sample; they hardly ever used psychedelics, but used heroin and cocaine more often.) (33)

The investigators who looked at the patterns of various drug used were also interested in the factors that might be responsible for this predictable order. Based on judgments of perceived safety (i.e., hazard to health) and availability, it was determined that both these attributes played a role in determining the rank order of use. Availability was more influential than safety, however; it was about five times as powerful a factor. (33) As an example of this process, marihuana headed the list for safety but alcohol was more widely used because it was seen as more available. Based on this tendency, one might expect use of a new drug to become more widespread if the substance is easily available, with a lesser effect on spread of use related to the perceived hazard of such use. The more sophisticated type of analysis illustrated here considerably enhances our knowledge of the basic processes underlying surface events and makes better prediction possible.

MARIHUANA USE BY STUDENTS

Student use increased in the country as a whole in 1972, but high school drug use may not be increasing at as high a rate as before. There continues to be wide variation in rates from school to school. (4, 31) Among all school studies reported, both high school and college, the proportions who ever used marihuana range from 6 to over 60 percent.

High Schools

In the first section of this chapter, the findings from a nationwide teenage survey and a West Coast community (San Mateo, California) were mentioned. Analysis of the nationwide survey is not yet complete, but details of the San Mateo data can be presented here.

The San Mateo series is now five years old. It shows a steady increase in annual use (any use in the preceding year) of marihuana at all grade levels. Overall, however, marihuana use appears to have stabilized at about 50 percent of the students in grades 10-12. Though use was slightly higher in 1972 than

in 1971, the rate of increase was distinctly lower in 1972. Stabilization also seemed to occur in the higher frequency of use categories. (See table below)

San Mateo County, California, Schools Grades 10-12[a], Percent Reporting Marihuana Use in the Past Year

Marihuana Use	1968	1969	1970	1971	1972
Any use during past year	31.9	39.5	42.0	49.7	51.0
10+ times during past year	17.5	24.4	26.3	32.9	34.5
50+ times	b	b	15.9	21.2	21.8

a - Blackford, 1972
b - Not collected

The levelling trend in the senior high school was also true in the junior high grades. A word of caution: There is some danger in considering those trends permanent ones. A levelling trend also appeared in the San Mateo figures between 1969 and 1970, but did not continue. Rates went up sharply the following year. (5)

Several other school systems have started annual series and now have second-wave results to report. A longitudinal study of personality, cigarette smoking, and drug use from 4th through 12th grade in Boston suburban schools has second-wave results. Those figures show a slight tendency for higher rates in 1972, but the two years' rates were not dissimilar. (34) Montgomery County, Maryland, an affluent suburb of Washington, D.C., has reported a doubling of rates, starting with the 9th grade, since 1969, a span of 3 years. The current figure is 40 percent reporting having ever used marihuana and 15 percent who report using it "regularly." (11)

Two high school studies are especially interesting because of the composition of the samples. One study examined drug use rates for three years in five Houston, Texas, schools with different ethnic composition. (6) The other study of interest was of high-achieving juniors or seniors listed in "Who's Who Among American High School Students" who responded to a mail questionnaire in 1971 (with 46 percent replying). (28,29)

The Houston study indicated that the two predominantly black schools were consistently lower than the other three schools in marihuana use in the three-year period. The two predominantly Anglo schools were highest, and the heterogeneous school with a large number of Chicanos was intermediate in use. Use

of marihuana was fairly stable over the three years, except for the two Anglo schools where there were significant increases. Rates were consistent by socio-economic status, also, the higher rates more typical of higher status. (6)

The high-achieving "Who's Who" students were surveyed in 1970 and 1971. (28) Although return rates were not as high as desirable in the two surveys, the results indicate that marihuana was in evidence as part of the behavior repertoire of many prominent high school students in both years. In 1970, 10 percent of those replying said they used marihuana then. In 1971, 13 percent reported using it more than twice. (21 percent had used it at least once.) (28)

The trends in marihuana use at the high school level are not as striking as in past years. The proportion who have ever used the substance nationwide has increased only slightly if at all. Undoubtedly in some schools it will continue to rise as the fad-like quality of the behavior dominates. In other schools, the rate seems to have stabilized. The situation should be watched closely in the coming year to see if this trend is a reliable one.

Colleges

As noted above in McGlothlin's estimates, college students' extent of use of marihuana was greater than that of any other group by mid-1972. The increase in percentage points from 1971 to 1972 also was greater for the college student group than for any other.

A major nationwide study of college students' life styles, including drug use, has reported changes in student rates between the 1969-70 and 1970-71 academic years. (Other factors investigated include concomitants of drug usage, institutional characteristics, and consequences of usage.) (32) Among a cohort of students in fifty four-year colleges across the country, large increases occurred in both marihuana and hashish use during that one-year period. In both years, the cannabis products were used by more students than used any of the other illegal drugs. The figures were as follows:

Percent of College Students Using Cannabis[a]

	1969-70		1970-71	
	Ever Used	Used During Academic Year	Ever Used	Used During Academic Year
Marihuana	27.6	23.6	41.6	37.3
Hashish	18.4	16.2	27.6	23.2

a - Rossi, 1972

Most other drugs besides cannabis also increased in use during the same year. It is not known how much overlap there might be among users of the various drugs. It should be noted that almost all those who had ever used either substance had used it during that academic year.

In an analysis of those who did or did not use cannabis in 1969-70 compared with those who did or did not use in 1970-71, it was found that more students were taking up use (21 percent of former nonusers) than were dropping use (11 percent of former users). The investigators estimated that a final "equilibrium" incidence of extent of exposure will be about 66 percent, based on analysis of current trends.

Another recent study of nationwide drug use rates, analyzed by type of college, reported that higher rates were associated with the following institutional traits: more selective (as to admission), larger, public, male, or nonsectarian. (14) Individual student characteristics associated more often with drug experience were: higher education or economic achievement of parents; liberal political affiliation; male; lack of active religious affiliation; certain academic majors (social sciences, humanities, or the arts); higher aspiration for an advanced degree; higher grade point average; and negative attitudes toward the war and government. Of the set of factors associated with drug experience, the authors found that anti-war activism, religion (lack of, or affiliation as Jewish), sex, and characteristics of the institution, were the strongest predictors of drug use. The characteristics listed above are not substantially different from those found in other studies of high school and college students. (26) The authors pointed out, however, that a wider "net" of predictors needs to be tested in such studies. (14)

By far the largest number of surveys of drug use available have been conducted with school or college populations. Some are sophisticated in design and analysis and add much to our understanding of drug use. Implications of some of these studies are found in the sections below on social aspects of use and personality characteristics of users. Some other school and college studies have been done with less thought and can at best only provide statistics of interest in the local area. Regardless of their limited applicability, these scattered studies do provide a "feel" for conditions. The rates vary quite widely, suggesting that in many areas students may be potential (not actual) drug users merely because of local conditions of drug supply, school ethos, contact with college populations, or other unknown forces. The results of all school surveys are consistent in showing increases by grade and in the order of "popularity" of illegal drugs. Marihuana is consistently the most popular and heroin the least.

MARIHUANA USE IN OTHER GROUPS

In the 1971 and 1972 Marihuana and Health Reports, research was reported from scattered studies of military populations, psychiatric patients, school dropouts, a group of occupations, hippies, Negro men in St. Louis, employed youth and ghetto youth. The highest rates of marihuana use found in that disparate set of studies were among hippies and school dropouts.

There are still relatively few studies of marihuana use per se among non-student groups. Military groups are an exception; several studies of service personnel, both in the U.S. and abroad, were published in 1972. Other than the military, the only new studies of special groups available are those on physicians, nurses, and nursing students.

In three surveys of health professionals, Lipp and his associates have found some surprisingly high rates of marihuana use. They are surprising, considering the values held by such groups and the risk to their careers of engaging in illegal behavior. The most surprising rate was the one reported for physicians -- four samples of A.M.A. members in New York City, San Francisco, upstate New York, and Nebraska. It should be mentioned that the return rate for the survey was rather low (only about half the sample), so these results must be interpreted cautiously. (21)

The proportion of physicians who had been "exposed to use" of marihuana was 37 percent; within this group, 25 percent had used it at least once; and 7 percent were using it currently. There were significant differences in use by age, younger physicians having used at a higher rate than older ones. There were also significant differences by geographic area: the New York City and San Francisco rates were higher than those in the other two areas. (21)

In two surveys of nurses and nursing students conducted at their national conventions, rates were lower than among the physician groups described above. Not surprisingly, nursing students had higher rates than nurses. Among students, 13 percent had used marihuana and 4 percent reported doing so currently. Among graduate nurses, 3 percent had used it, and only 1 percent were doing so currently. (22)

Military Use

Reports are now available on several well-conducted surveys of military populations made in 1971. Rates of use are reported here along with some description of individual characteristics related to drug use.

A large sample survey of all the Armed Services (enlisted) worldwide in 1971, produced an overall figure of 30 percent who had used marihuana in the preceding year. Among all who had used it, about half had used it less than ten times. About 40 percent of those using reported doing so several times a week or more. When asked whether they had used marihuana while on duty, from 3 to 16 percent reported having done so in the preceding year. Up to 45 percent in one branch said they had seen marihuana used on duty. (12)

More Army personnel used marihuana than did those in other branches of the Armed Services; Marine Corps personnel were next, then Navy and last, Air Force personnel. (These differences may reflect varying socio-demographic characteristics of those branches rather than conditions inherent in the institutions.) Rates of use were higher among younger enlisted men, at lower pay grades. Use was somewhat higher in Vietnam than at other service locations. Use by individuals in the service was highly related to former use in civilian life. (12)

Another large study of enlisted military personnel was done at Fort Lee, Virginia, in 1970. The group included military students (about 70 percent), support personnel, and instructors. Overall marihuana use reported totalled 44 percent; this figure represented all previous use of the substance and was not limited to use in the preceding year (as was the figure for enlisted men in the above study). All marihuana users were tabulated in three different groups, an analytic distinction that proved interesting in examining the correlates of the three types. One group (19 percent) consisted of persons who had used marihuana only and no other illegal drugs; a second group (also 19 percent), called multiple drug users, had used marihuana and other substances except heroin; the third group (6 percent) had used heroin, marihuana and may have used other substances. Among the "marihuana only" users, over half (52 percent) had used it only once or twice. (15)

All three of the drug-using groups differed in some respects from nonusers, in that they were more likely to be younger, single, educated, and of lower rank. They also had somewhat more convictions for various legal offenses (excluding traffic offenses). However, all three marihuana-using groups differed from one another too. The "marihuana only" group was somewhat older than the other two drug-using groups, better educated, and had fewer offenses. Heroin users, compared with the other two user groups, were the youngest, more likely to be non-white, had the least education, and more often had convictions for offenses. (15)

Several other studies of the military, in Vietnam and in Korea, were published in 1972. They reported marihuana use rates ranging from 20 to 40 percent of the groups surveyed. (35, 2) The majority of smokers who started in Vietnam did so in the first three months of their tour of duty.

One additional isolated finding is available to illuminate a different facet of the military's experience with marihuana. (30) It is a report on American soldiers in West Germany and their use of hashish in 1970 and 1971. According to that report, 46 percent of the soldiers had smoked hashish at least once; 16 percent had smoked it regularly three times a week or more often. (30) This rate is much higher than that estimated for the general population of the U.S. (20 percent of all marihuana use).

Taken altogether, the findings on military use of marihuana indicate that their rate of use is somewhat higher than the overall non-military rate. If age is taken into account, however, the differences would not be striking. Many of the characteristics of military users compared with nonusers are the same as those found in studies of the civilian population.

SOCIAL AND PERSONAL ASPECTS OF MARIHUANA USE

Earlier reports in 1971 and 1972 described other social aspects of marihuana use, such as peer or group support, that continue to be closely associated with use. Also mentioned earlier was the probability that potential users pass through several different stages in the process of becoming an actual user. A

fair number of new topics of interest have been explored and reported in detail during the past year: a study of information sources for decisions about marihuana; the roles of family and peers in drug use by young people; and drug dealing. Also, a longitudinal study of personality and drug use has reported some unique findings.

One study has focused on the sources of information used by elementary and secondary students in various stages of acquaintance with marihuana. (20) The sources of information about marihuana mentioned most frequently by all students in the study were parents, television, and friends. But there were distinct differences in the types of sources accepted by students at various grade levels. For 5th graders, television and parents were most significant; for 7th graders, friends and television; and for 11th graders, friends and other students played the largest role. In general, younger children use more socially approved sources compared with older students (who tend to rely on "non-authority" sources). The authors commented that many students appear unaware of the influence process surrounding their decisions about marihuana use. (20)

Parents and Peers

Three studies have investigated the relationship between adolescent use of marihuana and use of marihuana and other drugs by parents and peers. Two of the studies were conducted on adolescents between 12 and 17 years of age, in an interval of several years. One study confirms the crucial role of peers in adolescent drug use. (18) Adolescents' use of marihuana is directly related to the best friend's self-reported drug use. An adolescent's marihuana use is also related to the proportion of friends reported to have used marihuana. When none of the adolescent's friends used marihuana or other drugs, only 7 percent of such youngsters were found to use it themselves. By contrast, when all their friends reported use of marihuana, 92 percent had also used it. Similarly, adolescents are more likely to be users (76 percent) if their brothers and sisters are users, and to be nonusers (38 percent) if their siblings have never tried marihuana.

Results from another study also underscore the strong influence of peers on an adolescent's drug use. (10) Data from the Columbia study of teenage drug use indicate that drug users in all grades were much more likely than nonusers to report having at least a few close friends who use one of the following drugs: marihuana, amphetamines, LSD, barbiturates, or heroin. Eighty-seven percent of the drug users reported that their friends also used marihuana, while only 4 percent of the nonusers had such friends.

Adolescent use of marihuana is related not only to the best friend's use, but also to the frequency with which the friend has used marihuana. Drug use is also directly related to the frequency of mere contact with peers and to being peer-oriented rather than parent-oriented. (18) Marihuana users are more likely to be found among students who visit with their friends on a daily basis, among those who would continue to see their friends over their parents' objections, or among those who respect their friends' opinion over their parents', when confronted with a problem. Similarly, these users are found

to rely on peers and contemporaries as sources of information about drugs, while nonusers are reported to have learned (or obtained most of their knowledge) from their parents, mass media or the school.

Both parents' and best friends' drug use have an independent effect on the adolescents' marihuana use. The effect of peers, as illustrated, is larger than that of parents. Lowest rates of marihuana use are found to occur when neither the parent nor the best school friend have used psychotropic drugs, and the highest rate (71 percent) is found when both have used them. (18)

In addition to the influence of peer drug use on an adolescent's marihuana use, perceived, as well as self-reported, parental use of psychotropic drugs has been shown to have a profound effect on an individual's drug use. These data report that there is a minimum of 50 percent increase in the rate of marihuana use among those individuals who report that their parents are users of psychoactive drugs, as compared with those who do not report parental drug use. Associations based on the adolescent's perceptions of behavior are more than twice as high as the associations based on parental self-reports, or parental actual drug use.

Data also indicate that parents tend to deny the extent of their children's drug use and that they are ineffective in enforcing parental rules concerning drug use.

Results from a study of family factors indicate that drug use is part of a constellation of beliefs and practices related to the child-rearing goals and personal beliefs of the parents. A study of white, black and Mexican-American families indicates that there are certain factors that increase the probability of drug use in children. These characteristics include: lack of cohesion in the family, use of alcohol and medications by parents, and less emphasis on self-control. Families which tend not to encourage drug use are characterized as cohesive, support authority in the home, and are generally more content. (8)

Drug Dealing

The subject of dealing or selling marihuana illegally has received little consideration in previous reports on marihuana use. Dealing is ordinarily viewed as a separate phenomenon from using. Recently, however, research on the West Coast has shown that marihuana dealers are marihuana users, and that dealing is encouraged in a social context, with friends and peers. (7) The typical marihuana dealer is not a street dealer of hard drugs such as heroin or cocaine. He is reported to be middle class, in his twenties, not involved with criminals and rarely delinquent in other ways. The dealer is generally a user and selling is largely a function of the amount he uses.

The extent of use significantly affects the amount a dealer sells. Sales are most frequently made between friends or acquaintances. Among those using every day, 96 percent had sold, while among those using less than once monthly, only 29 percent had sold. Selling marihuana is also associated with the extent of multiple drug use, as well as involvement with a drug centered subculture. While 13 percent of those who had used only marihuana had also sold it, 64 percent of those who had used three or more other illicit drugs had done so.

Selling marihuana is also linked to the number of close friends who are regular smokers. Among those who claimed 60 percent or more of their friends were users, over two-thirds sold marihuana. Of those claiming between 29 percent or less of their friends used marihuana regularly, only 21 percent sold the drug.

The dealer is usually a distributor and provides marihuana to his friends through informal transactions. Dealing is common and reportedly widespread, and the transition from experimenter to user to dealer is often rapid. The process is more likely to occur if the user enjoys drugs and risk taking. The probability is further increased if his friends are regular users. Other factors which contribute to regular marihuana dealing include an interest in money, desire for peer approval and prestige, and a willingness to violate the law. Additional findings also indicate that selling is associated with an avoidance of traditional work and experimental life styles.

Most regular marihuana users are reported to have been involved in dealing at one time in their lives. Cannabis was also found to be the preferred drug by dealers. Most reported experiences with both marihuana and hashish. Daily use remained constant for approximately 44 percent of all users after age 19.

Investigation of high school marihuana sellers shows that marihuana was the first illicit drug used by 68 percent of these individuals. Dealers stated that they had sold off-campus as well as on, although they did not necessarily always sell to fellow students. On-campus sales were reported more frequent, and most customers were friends or acquaintances of the seller.

Marihuana users or dealers were not found to be common among junior high school students. Drug use by young teenagers is primarily social and usually occurs at home. Only 10 percent of junior high students using marihuana indicated that they obtained their supply from a "professional dealer." Supplying drugs to other students was reported by about one-fourth of the junior high school students.

An interesting finding in this study was that many dealers believed that there should be regulation or criminal statutes for opiates, amphetamines, barbiturates, hallucinogens, tranquilizers, alcohol and tobacco, but not for marihuana. The rationale given for control of these other substances was that all the other drugs (except cannabis) are known to be potentially harmful. Another reason some dealers supported the need for regulation of harder drugs was to assure purity of the preparation.

Personality Predictors

The social and demographic correlates of marihuana users compared with nonusers have been reported frequently, and they tend to be fairly consistent (see above). No study so far has been able to show whether there are other personal characteristics existing prior to initial drug use that would give clues to susceptibility to use of marihuana. One study now has preliminary data to report on one group of junior and senior high students' and their characteristics before they experimented with drugs. (34)

According to the study of students in six selected school systems near Boston, in 1969, a small number of characteristics were quite in evidence among students who later, in 1972, would use marihuana. (Data were available on students as early as the 4th grade.) Among these characteristics were: rebelliousness, low grade point average, cigarette smoking, and favorable attitude toward cigarette smoking.* Among these, rebelliousness toward authorities and rules was the strongest predictor. All of these characteristics were more true of marihuana users than nonusers, and more true of heavier users than of lighter users. (34) As this study progresses, more findings will be available to describe later experimenters and those who discontinue use.

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* Attitudes toward drugs were not measured in 1969.

Bibliography

1. Anon. Drug Use Among Nation's Youth Explored in Study; Many Drugs Rejected, Marihuana Attitudes Divided. In Institute for Social Research Newsletter, Ann Arbor, Michigan, Spring 1972, pp. 4-5.

2. Baker, S. L., Jr., Drug Abuse in the United States Army. Bulletin of the New York Academy of Medicine, Vol. 47,541-549, June 1971.

3. Berberian, Rosalie M., "Drug Use among Adolescents." Paper presented at the annual meeting of the American Public Health Association, Nov. 14, 1972.

4. Berg, Dorothy, & Broecker, Linell, Illicit Use of Dangerous Drugs in the United States, June 1972, Bureau of Narcotics & Dangerous Drugs, Washington, D.C.

5. Blackford, Lillian, "Preliminary Report, 1972, San Mateo County, California, Surveillance of Student Drug Use," San Mateo, California, May 24, 1972, (NIMH Grant DA 00094).

6. Bloom, Robert, J. Ray Hays, and G. Michael Winburn. Marijuana Use in Urban Secondary Schools:a Three Year Comparison. 1972. Texas Research Institute of Mental Sciences, Houston, Texas, submitted for publication.

7. Blum, Richard, The Dream Sellers, 1972, San Francisco: Jossey-Bass Inc., 1972.

8. Blum, Richard H., & Associates, Horatio Alger's Children, San Francisco; Jossey-Bass, Inc., 1972.

9. Dvorak, Edward J., A Longitudinal Study of Non-Medical Drug Use Among University Students: A Brief Summary, Journal of the American College Health Association, Feb. 1972, Vol. 20, No. 3, 212-215.

10. Elinson, Jack, A Study of Teen-Age Drug Behavior, Columbia University School of Public Health, New York, N.Y., NIMH Grant DA-00043, Progress Reports, 1971-72.

11. Elseroad, Homer, and Goodman, Samuel, "Teenager's Attitudes Toward the Use of Drugs, Alcohol and Cigarettes: Findings of a Survey Conducted in January 1972, Among Students in Grades 7 through 12 of the Montgomery County, Maryland, Public Schools," August 31, 1972.

12. Fisher, Allan H. Jr., "Preliminary Findings from the 1971 DoD Survey of Drug Use," March 1972, Human Resources Research Organization, Alexandria, Virginia. Technical Report No. 72-8.

13. Fisher, Allan H., K. Eric Nelson, & Jacob Panzarella, "Patterns of Drug Usage among Vietnam Veterans," May 1972, Human Resources Research Organization, Alexandria, Virginia, Professional Paper, No. 12-72.

14. Gergen, Mary, Kenneth Gergen & Stanley Morse, Correlates of Marihuana Use Among College Students. Journal of Applied Social Psychology, 1972, Vol. 2, No. 1, 1-16.

15. Greden, John F., & Donald W. Morgan, Patterns of Drug Use and Attitudes Toward Treatment in a Military Population, Archives of General Psychiatry, Feb. 1972, Vol. 26,113-117.

16. Goode, Erich, Cigarette Smoking and Drug Use on a College Campus, The International Journal of the Addictions, Vol. 7, No. 1, 133-140, 1972.

17. Grupp, Stanely, E., Marihuana Use and Emergent Drug-Use Patterns. NIMH grant MH-14157, MH-17196.

18. Kandel, Denise. "Adolescent Marihuana Use and Interpersonal Influences." Paper presented at the annual meeting of the American Sociological Association, August 1972.

19. Kandel, Denise. Family Processes in Adolescent Drug Use, NIMH grant DA 00064. Progress report, 1972.

20. Kowitz, Albert & Richard Clark, Ways Youth Receive Information about Marihuana, NIMH DA 00144, Final Report Summary, July 31, 1972.

21. Lipp, Martin & Samuel Benson, Physician Use of Marihuana, Alcohol, and Tobacco, American Journal of Psychiatry, Vol. 129, No. 5, Nov. 1972, 612-616.

22. Lipp, M. R., S. G. Benson, & P. S. Allen, Marihuana Use by Nurses and Nursing Students, American Journal of Nursing, 2339-2341, December 1971.

23. McGlothlin, William H., Marihuana: An Analysis of Use, Distribution and Control, Contemporary Drug Problems, Vol. 1, No. 3, Summer 1972, 467-500.

24. McLeod, Jonnie, and Gloria Grizzle. "Alcohol & Other Drug Usage Among Junior and Senior High School Students in Charlotte-Mecklenberg," Prepared for Community Drug Action Committee, Charlotte-Mecklenberg, North Carolina, June 19, 1972.

25. Marihuana and Health, A Report to Congress from the Secretary U.S. Department of Health, Education, and Welfare. Subcommittee on Alcoholism and Narcotics of the Committee on Labor and Public Welfare, United States Senate, Washington; D.C.; U.S. Government Printing Office, 1971.

26. Marihuana and Health. Second annual report to Congress from the Secretary of Health, Education, and Welfare. Subcommittee on Alcoholism and Narcotics of the Committee on Labor and Public Welfare, United States Senate, Washington; U.S. Government Printing Office, May 1972.

27. Marihuana: A Signal of Misunderstanding, First report of the National Commission on Marihuana and Drug Abuse. Washington, D.C.; U.S. Government Printing Office, March 1972.

28. Merit Publishing Company. "Second Annual National Opinion Survey." 1971. Northfield, Illinois.

29. Merit Publishing Company. "Survey of High School Achievers." 1970. Northfield, Illinois.

30. Rensberger, Boyce, Moderate Hashish Use Found to Cause Few Ills, New York Times, Friday, July 7, 1972.

31. Research Triangle Institute. NIMH Contract HSM-42-72-169. Survey of Current Studies.

32. Rossi, Peter. Study of Life Styles and Campus Communities. Department of Social Relations, Johns Hopkins University, Baltimore, Maryland, NIMH grant DA 00156. Progress Report, 1972.

33. Sinnett, E.R., K.S. Wampler, & W.M. Harvey, Consistency of Patterns of Drug Use, Psychological Reports, 1972, Vol. 13:143-152.

34. Smith, Gene, Drugs and Personality, NIMH grant DA 00065. Progress Report, 1972.

35. Stanton, M. D., Drug Use in Vietnam: A Survey Among Army Personnel in the Two Northern Corps, Archives of General Psychiatry, Vol. 26:279-286, March 1972.

35b. Sussman, Ralph. personal communication, National Commission on Marihuana and Drug Abuse.

36. Wallach, Amira. Varying Fates of Young Drug Users, Pre-publication draft of paper presented at Meetings of the California State Psychological Association Annual Convention, Coronado, Jan. 1971.

37. Zanes, Anne. Personal communication concerning NIMH grant DA 00043, A Study of Teen-age Drug Behavior, School of Public Health, Columbia University, New York, N.Y.

MARIHUANA USE IN OTHER COUNTRIES

Introduction

The herb that Linnaeus named Cannabis sativa over two centuries ago originated somewhere in the desert regions to the south and east of the Caspian Sea. (6) Today it grows in almost all countries of the world, in a wide variety of climates and physical environments, ranging from the equator north to 60 degrees latitude. This adaptability is due, almost certainly, to human intervention over a long period of time. Human exploitation of cannabis is thought to reach back as far as 6,000 years, with actual cultivation beginning only slightly more recently.

Although the common name hemp has come to be associated with this genus and species, there are actually more than twenty plant families that produce products known as hemp. It is this fact, in addition to the botanical name changes it has undergone over time, that make it so difficult to trace a true ethnobotanical history of cannabis - not only that which is grown for fiber and other industrial uses, but also that which is cultivated for its known pharmaceutical properties.

In the fifteenth century B.C. (6), the Chinese book known as the Rh-Ya was compiled and in it there is mention of the herb Ma, the Cannabis sativa plant. Not only were the fibers and the potent resins employed at the time, but the Rh-Ya describes the first ritual of shamanistic use of the plant. The most detailed early account of the uses of cannabis in early China is to be found in the Shu-King, written in 500 B.C. It was the practice of the early Chinese to carve the main stem of the plant into the likeness of a serpent coiled around a rod (something like the symbol of the caduceus). This image was used in curing rituals; a relative of the patient beat on the sickbed with the snake rod in order to dispel evil spirits. In the second century of the Christian era, at least one celebrated Chinese physician performed surgery using cannabis resins mixed with wine as an anesthetic.

The ancient Mediterranean peoples were well acquainted with the use of various narcotic plants, such as the opium poppy, mandrake, henbane, deadly nightshade, as well as cannabis. There is a classic Greek term cannabeizen (6), which means to smoke cannabis. This smoking frequently took the form of inhaling vapors from an incense burner in which these resins were mixed with other resins such as myrrh, balsalm, frankincense, and perfumes.

The Greek historian Democritus (ca., 460 B.C.) knew cannabis as potomaugis, and said that it was drunk with wine and myrrh to produce visionary states. The first Greek botanist, Theophrastus (310-287 B.C.), wrote of cannabis under the name dendromache, and gave one of the first accurate accounts of the plant.

Lucilius was the first Roman writer to give an account of the plant, ca., 100 B.C. The fiber of the plant was highly esteemed as cordage in most of the early vessels. According to Emboden (6), the fiber also had a prominent

place in mythology: it was said to be the stuff that Penelope wove and tore apart to discourage her suitors during the absence of Ulysses.

The famous physician Galen (A.D. 130-200) spoke of cannabis as a medicinal, but he also recorded non-medicinal, non-ritualistic use of cannabis mixed with wine to be used as a final course at a banquet. Strangely enough, the ancient Egyptians seem to have known nothing of the plant and any of its various uses.

There is historically documented use of cannabis in the funeral customs of the ancient Scythians, a nomadic people who ranged eastward as far as what is now central Siberia. (6) The Soviet archaeologist, S. I. Rudenko, discovered archaeological evidence of the use of Cannabis sativa to induce trances in Scythian funeral rites during his excavations of the great burial mounds (kurgans) at Pazaryk in the Altai, between 1947-51. Rudenko found metal support rods and bronze censing vessels containing not only stones which had been heated to produce hemp-seed vapors but even the seeds themselves, some of them burnt.

The Scythians seem to have become acquainted with the ritual use of cannabis when they were defeated in battle by the Thracian Getae early in the sixth century B.C. The shamans of the Getae used hemp smoke to induce visions and oracular trances. In the Scythian funeral rites the mourners rolled heated rocks from the funeral fires and placed them in censers. Hemp seeds were then thrown on the rocks and the resulting vapors were inhaled. Some other accounts dating from about the same time say that the smoldering herbs were covered with large skin blankets, which were lifted at intervals so all could inhale the vapors.

In a study done in 1936, a Polish linguistic scholar (Bentowa, now resident in the United States) compiled a list of more than 100 synonyms for the cannabis plant. (6) She began by studying all the words meaning hemp in Indo-European, Finnish, Turkish and Tartar languages, and Semitic language groups, and then, having eliminated the obviously borrowed words (whether they were Finnish, Turkish, Celtic or Roman), she was left with four groups of languages to investigate - all of which had remarkably similar words for the plant cannabis. They are Sanskrit, cana; Slav, konopla; Semitic, for example, in Assyro-Babylonian, kannab; Greek, cannabis. In all these languages the words meaning hemp have a common root, kan. This root with the double meaning of "hemp" and "cane" is common to almost all the languages of antiquity.

The ending "bis" can be found through study of several Semitic texts from Oriental antiquity. In the original text of the Old Testament and its Aramaic translation (the Targum Onculos) the word "kane" or "kene" sometimes appears alone, and sometimes linked with the adjective "bosm" in Hebrew or "busma" in Aramaic, which means aromatic, to smell good. Both the Biblical kane bosm, and the Aramaic kene busma mean hemp. The linguistic evolution of the term in question leads to the formation of the unique term kanabos or kanbos. The Mischna, the collection of traditional Hebrew law which contains many Aramaic elements, contains the term kanabos. The astonishing resemblance between the Semitic kanbos and the Scythian cannabis may be proof of the fact that the Scythian word was of Semitic origin. Historical evidence would seem to give

credence to the hypothesis drawn etymologically. The Iranian Scythians were probably related to the Medes who were neighbors of the Semites and could easily have assimilated the word for hemp.

By the tenth century A.D. cannabis was well-known throughout the Mediterranean and Arab worlds. (2) The use of the drug was not prohibited by Mohammed (570-532) although alcohol was. Even so, some African Moslems have banned its use on religious grounds, while most of the rest of the Moslem world has not. Legal restraints have been comparatively recent, dating from the nineteenth and twentieth centuries.

According to modern Arabic historians (9), cannabis came to be planted and used in Egypt around the mid-twelfth century A.D. In that country, as in India, the plant seems to have aroused controversy from the very beginning; at least three different groups of writers took part in the arguments: 1. those who were for hashish and against alcohol; 2. those who defended alcohol against hashish; and 3. those who condemned both.

Poems from the tenth to thirteenth centuries describe the behavioral changes attributable to hashish; those considered most desirable have a strangely modern ring to them. They include euphoria, sociability, feeling of being important, feeling of being carefree, meditativeness, activation of intelligence By way of comparison with alcohol the writers pointed out that it was cheap, not prohibited by the Islamic religious authorities, required a comparatively small quantity to achieve the desired effect, had a smell which was not easily detectable, and was never pressed by the feet (as the grapes were) to be made ready for consumption. The opponents of hashish presented a series of arguments which could easily be transposed to the current scene. Hashish use causes submissiveness, debility, insanity, some sorts of organic brain damage.

In the seventeenth century A.D., a comprehensive Arabic pharmacopoeia was published by Daoud Al Entaqui in which the author mentioned cannabis under the Persian name Shahdang. The author prescribes the drug for the treatment of various somatic conditions, but he also mentions the psychotropic effects - euphoria, lethargy, sensory debilitation, and temporary sexual potency tailing off eventually into impotence. Such writings are still consulted by certain segments of Egyptian society.

It is probable that the most likely route of migration for cannabis into India is by way of Iran, since modern botanists believe that the plant is not indigenous to the country. (6) It may be that prior acquaintance and use of plants with tranquilizing properties such as Rauwolfia serpentina, and sedative properties such as Withania somnifera facilitated the easy acceptance of cannabis.

The earliest Indian uses seem to have been religious, and there are many legends indicating that it was a holy plant to some Hindus, just as peyote is today to many North American and Mexican Indians. The first medical uses of the plant seem to have dated from about the twelfth century A.D.

There is little firm documentation concerning the routes by which cannabis entered the African continent as a whole, but presumably it could have come by way of India or Saudi Arabia. In addition, there was differential diffusion,

depending on the particular part of the continent and its openness to conquest, and/or trade by other countries. To cite but two examples, reports from Ghana state that the use of cannabis "wee" is not indigenous, that it is not known to native herbalists as a therapeutic, and is not used in any native religious ceremonies. All reports indicate that its introduction was comparatively recent, probably around the end of World War II. On the other hand, there are reports from South Africa, dating from the end of the seventeenth century, that the first Dutch governor found cannabis (called "dagga") already in use by the Hottentots and Bushmen. European visitors to the Congo in the late nineteenth century noted vestiges of cannabis usage among the Baluba, a Bantu speaking tribe of the Belgian Congo. The Balubas subjugated many other tribes (6) and extended the use of cannabis to them. This extension of use was a matter of policy on the part of the conquering Balubas, since cannabis religious usage was intended to replace the other religious practices and tribal gods in the conquered territory.

Knowledge of the use of cannabis by various indigenous groups located in different sections of Africa is of interest not only in regard to that continent itself, but also in regard to the supposed diffusion to the New World of this practice by Negro slaves. A great deal is known about the parts of Africa from which slaves were recruited for service either in North or South America or the Caribbean Islands, but to our knowledge no one has attempted a systematic study to attempt to determine the linkage between the parts of Africa from which these slaves came, and the particular parts of the New World to which they were sent and their supposed introduction of cannabis.

For example, most observers agree that there was no knowledge of the psychotropic, or even the possible medical uses of hemp in American plantations which employed many Negro slaves. However, the American colonies, particularly before the time of independence, were major growers of hemp (to be used for ship cordage) for the mother country. In Brazil, on the other hand, with no growing of hemp, but rather concentration on such crops as sugar, many writers feel that cannabis was introduced by way of slaves.

The route of introduction of cannabis into Europe is very obscure. Although usage was certainly noted in Arab countries as early as the time of the Crusades (in fact this is the date of the legendary Hasan, from whose name both the terms hashish and assassin are said to have been derived), there seems to be no record that the Crusaders either used this drug themselves while far from their homelands, or that they carried knowledge of its psychotropic or therapeutic properties back with them to Europe. Similarly, to our knowledge, there has been to date no published accounts of the extent to which Arabic medicine, introduced into Spain certainly at the time of the Moorish conquest and undoubtedly much earlier, introduced at the same time a knowledge of the therapeutic uses of cannabis.

The drug was mentioned by Prosper Alpino in his book De Medicina Aegyptorum as early as the sixteenth century (9), by Rumph of Hanau in Herbier d'Amboyne towards the end of the seventeenth century and, of course, by Linnaeus slightly after the mid-eighteenth century. The surgeons and physicians attached to Napoleon's army during the invasion of Egypt in the early 1800's

became acquainted with the use of cannabis as part of the Arabic medical armamentarium. However, the first book which attempted to explore the therapeutic uses of cannabis dates back to 1845 with a publication of a book by Dr. Jacques Moreau of the Hopital de Bicetre.

Moreau was one of the first modern psychiatrists to experiment with psychotropic drugs in the treatment of mental illness, since he had used datura for his patients and later substituted cannabis. Moreau was also one of the first persons to describe the variety of drug effects which might be obtained from hashish, emphasizing that the differences in effect could be due to personality, physical condition, motivation, self-control, dosage, setting, mixture with other drugs (he described, for example, the Arabian practice of mixing hashish with opium and datura), expectations of effect.

Moreau seems to have been unsuccessful in inducing his medical colleagues to experiment with the drug, but he did succeed in introducing a group of artists and writers to its use, and this led to the formation of the famous Club des Haschischins.

Members of this Club (particularly Baudelaire and Gautier) wrote extensively of the mood-altering effects of the drug (which, interestingly enough, they did not smoke, but used in the form of a sweetmeat Dawamese, just as it had been used by Arabs for hundreds of years). Further, the accounts of the meetings of the Club suggest a strongly ritualistic character. Meetings were held monthly (almost like regularly scheduled religious services) with flickering lights, ceilings painted with mythological scenes, appropriate music. It is interesting that Baudelaire had been to India but apparently had not learned of its religious or medical use there, but became acquainted with it in France through the introduction of a medical man (Moreau) as well as his fellow artists and writers.

It should be remembered that the European world, at least certain sections of the avant-garde, had had an extraordinary interest in the Orient and the Middle East from the end of the eighteenth through the middle nineteenth centuries. A whole movement, known by literary historians as Orientalism, took place about this time, and many classics of the literature of India, Persia, and the Middle East were translated and adapted into various European languages. (It was during this period that the first translation of the Arabian Nights appeared.)

It is perhaps understandable then that the Parisian writers and authors, introduced to the knowledge of cannabis through a psychiatrist, should have seized upon and exploited the mystical (oriental), consciousness altering qualities of the drug, and to have been comparatively unconcerned about its medical and therapeutic uses.

In England, however, even more exposed to the influence of the Orientalists (since the Institution of the Asiatic Society of Bengal came about in 1784 and the Royal Asiatic Society of Great Britain in 1824) knowledge of cannabis came with emphasis on its therapeutic, rather than mind-expanding uses. The interest in the possible medical uses of cannabis was initiated by the work

(in 1838) of Dr. W. B. O'Shaughnessy, a professor of chemistry in the Medical College of Calcutta. He used it in the treatment of patients suffering from such diverse ailments as rabies, rheumatism, epilepsy and tincture of hemp. He also found that tincture of hemp was an effective analgesic, and to have anti-convulsant and muscle relaxant properties.

O'Shaughnessy's work kindled widespread interest in England, the United States, as well as many non-English speaking countries, and physicians experimented with the use of cannabis (in various forms but not as smoking material) for a wide variety of ailments. Interestingly enough, there were few reports of the so-called mind-altering or euphoriant effects of the drug although there were many articles on the therapeutic efficacy of cannabis published during the last forty years of the nineteenth century. However, we were well along in the current upsurge of psychological research dealing with the psychotropic drugs before the full importance of expectation as a critical variable was recognized. It should be remembered that the nineteenth century physicians were not unaware of the possibilities of the mind-altering effects of drugs; after all, they were familiar with the uses of morphine, and not only as a potent painkiller.

It is tempting to speculate on what the results might have been if cannabis had been smoked instead of being used in other forms since smoking, in most of the developed Western world, had long since become associated with the production of a sense of well-being. In fact, many authors attribute the phenomenal spread of the use of cannabis not only to the inherent properties of the drug itself, but to the fact that smoking of tobacco introduced many persons to the notion that it was possible to attain a sense of well-being in some other way than through the use of beverages. In addition, in many parts of the world where use of cannabis is well entrenched, cannabis and tobacco are mixed together.

Tobacco itself has a history which is almost as curiously mixed (used in a variety of settings, for a variety of purposes) as cannabis. It was a sacred plant to North American Indians, and at the time of the early English settlers was not used in a secular context. Either as a beverage or as smoking material, nicotine is still used by some primitive South American Indian groups for ritual purposes, divination, and healing. Some writers claim that ingestion of huge amounts of nicotine (particularly some of the strong varieties found in some parts of South America) can lead to hallucinatory experiences, although this is still a matter of dispute.

Cannabis and nicotine also share a long history of strongly held divergent views about their value; when tobacco was introduced into Europe, it was hailed by some as a universal nostrum, and by others as a spawn of the devil. Moreover, early accounts of the introduction of tobacco into Europe show that the first persons to take up the habit were regarded as avant-garde members of their society, and a certain amount of ritual (including special classes to teach young gentlemen how to blow smoke rings) came into being. As the habit spread, however, and diffused to members of all social classes, the ritual character disappeared, the types of persons using (except perhaps for females) became indistinguishable from the nonusers. Much the same thing

seems to be happening with respect to cannabis users in industrialized Western countries.

Even in countries where cannabis use has long been a settled habit among members of the lower classes, a good case can be made that present day use by youngsters from the middle and upper classes is not a matter of emulating lower class citizens at home, but rather their counterparts in more highly industrialized countries. It is no accident that in some countries (Chile, for example) where the use of cannabis is not indigenous, the spread of the habit is being fought not only on moral but also on patriotic grounds.

Cannabis is not indigenous to the New World, and there is no firm documentation on exactly how the plants, prized for their psychotropic qualities, first entered this continent. Accounts are clear, however, concerning the dates for the introduction of hemp plant cultivation into both Canada and the United States, and in both countries this introduction came very early in the colonial period. Most observers agree, however, that cannabis as an intoxicating drug was introduced into the United States by way of Mexico.

There is no mention of cannabis in all the accounts of North American Indian medicine assembled by early travelers (some of them physicians) to this continent. There is also no evidence that the early settlers, who borrowed many folk remedies from the Indians, had ever heard of the possible medicinal properties of this herb. There is ample evidence, of course, that they enthusiastically (for the most part) adapted the cultivation and use of tobacco, which was considered sacred by the Indians because of its wonderful qualities.

In the extensive collection of materials on Aztec Material Medics assembled in Mexico by Sahagun shortly after the Conquest, one finds no mention of the herb. Similarly, no accounts of cannabis appear in the documentation regarding the Inca territory although there is extensive discussion of coca (which incidentally, has served and continues to serve almost as wide a variety of uses as has cannabis itself).

The plants may have been introduced by the Spaniards to Mexico, Central and South America, either at the time of the Conquest or shortly thereafter. It should be remembered that not only had Spain been occupied by the Moors, but that Arabic medicine was held in high repute throughout the world. On the other hand, there seems to be no published documentation of its employment by any of the Spanish surgeons and physicians who accompanied the early Conquistadores. There is every evidence, on the other hand, that the Spaniards continued to employ the chief intoxicating drug of their homeland, alcohol, in the New World and some of their earliest efforts were directed to viniculture.

Negro slaves were early employed in Spain and Portugal (even before the Conquest) and it may be that some of them knew of the use of the plant. In Brazil, the words for cannabis (which include maconha, liamba, diamba) are closely linked to some words for the plant used in various sections of Africa. But accounts of early employment of the plant as a medicinal are strangely lacking, even though there has been extensive documentation of the contribution

of the slaves to the knowledge of the utilization of various plants both as healing herbs and as standard elements of the distinctive Brazilian cuisine.

Negro slaves were recruited for service in the New World from various parts of Africa, and some sections of that vast continent knew of the uses of cannabis before the tremendous expansion of the slave trade. To date, however, even with the burgeoning literature on African survivals in the New World (which was inspired by Herskowitz in great part), there has been no published documentation on the route of diffusion of cannabis to the New World.

It should be borne in mind also that, with the exception of the Rastafarians in Jamaica (who learned of cannabis use through its introduction by East Indians), there seems to be comparatively little use of cannabis by religious groups which show the strongest evidence of African Negro ancestry. This is true of cults which stress possession such as Candomble in Brazil, Shango in Trinidad, Vodun in Haiti.

The method of use of cannabis has a great deal to do with whether it is used in a social-secular context (as a recreational drug, or as work adjunct) almost exclusively, or whether it still retains part of its religious character because of its use in a ritual setting.

The use of the plant for medical and religious purposes, to aid in the performance of work (either to stimulate or to allay feelings of fatigue), probably preceded its use as an intoxicant. Even today, for many, if not most of the users in various parts of the world, the value of the drug lies primarily in its use in medical practice, including self-medication, in religious rites (many of them concerned with petitions for aid in curing illness, or pleas for help to maintain health) rather than as an intoxicant.

In many countries cannabis has been, and continues to be used, for religious purposes, for example, India, among certain cult groups in Central and South Africa, Brazil, Mexico and Jamaica. In India, according to the Indian Hemp Commission report, it was bhang, the weakest variety of the plant, which tended to be used in religious ceremonies. In other countries (some parts of the Near East, at least one section of Mexico, among the Rastafarians in Jamaica) a stronger variety - ganja or hashish - may be employed.

It is not possible to give a fully documented current history of the therapeutic uses of the plant, since ethnohistorical, anthropological, and sociological and economic research concerning the using populations and the uses to which the drug is put has lagged far behind the pharmacological and biochemical. In India, the uses of cannabis both in traditional folk medicine, and in the more classic theories of medicine have been fairly extensively documented.

Both opium and cannabis have been employed as therapeutic agents by the Ayurveda and Unani Tibbi systems of medicine in India for over ten centuries. (2) Apparently both agents were known and employed as folk medicine even earlier - as early as the fourth to third century B.C. During the last two centuries,

traditional folk medicine and the classical Indian medicine have become almost synonymous.

Both the Ayurvedic and Unani Tibbi systems apparently introduced both cannabis and opium into their medical armamentarium as a result of borrowing from Arabic medicine, brought to India about the ninth century A.D. by the Muslims. Today the medical needs of well over one-half the population of India (especially rural India) are attended to, almost exclusively, by practitioners trained in these two traditions. It has been estimated that there are about 500,000 Ayurvedic physicians in the country. To bar the use of opium and cannabis to these physicians would mean that there would be a vacuum created in medical service, because it will be a long time before modern doctors can be persuaded (in any great numbers) to practice in rural areas. (2)

Cannabis has been used, and continues to be used, in many parts of the world as a stimulus, to prevent fatigue, in a sense as a work adjunct. This is true in India, South Africa, Jamaica, parts of Mexico, and undoubtedly in other places where full documentation is still to be forthcoming. The earliest users in the United States seem to have been the stevedores, and Mexican immigrant farm laborers. Whether, in fact, cannabis does serve as a stimulant and actually aids in the performance of physically demanding labor, in the manner of the true stimulants, is a matter which has not been fully settled. In a later section of this report dealing with the study of chronic cannabis users in Jamaica, we comment more fully on this phenomenon. The Canadian government report suggests that it is advisable to directly test the theory by initiating a series of performance tests for athletes.

It is illuminating to note that a good deal of the research having to do with cannabis and its effect on work performance and work habits has been carried on in highly industrialized Western societies, where the amount of sheer physical labor required by the working force is being successively reduced through the introduction of labor-saving devices.

It should be borne in mind that the drug has been and continues to be used in many countries, not only for the treatment of purely somatic complaints, but also those which seem to be more emotionally based. For example, in India cannabis is used to treat insomnia, nervous irritability, and to stimulate appetite, as well as for dysentery, neuritis, and upper respiratory complaints.

The foregoing brief summary of the history of cannabis use and diffusion points up not only the comparatively sparse amount of knowledge concerning the social and cultural concomitants of cannabis use, but also the necessity to involve more social scientists (historians, anthropologists, sociologists, economists, psychologists) in its study.

From the published reports, even though they are admittedly insufficient, the picture seems to be this. Until the present time (when the use of cannabis has spread to the middle and upper class adolescent in the traditional cannabis using countries as well as the more industrially advanced Western nations) the typical cannabis user tended to be a young male, usually from a lower socioeconomic background. The user could be found in urban or rural (note studies from Egypt and South Africa) areas.

In a series of articles emanating from Nigeria in the fifties and sixties, Lambo has pointed out the possibilities for cannabis diffusion with the rise of industrialization because many workers are transients, moving from one big construction project to another, either within the borders of their own country or outside it.

World War II as well as all the wars since then have also tended to spread the knowledge of cannabis use, especially to the age cohort which has always been most attracted. The use of cannabis by United States Forces in Vietnam has been well documented. Israel reports that some of her citizens have become acquainted with the use of hashish as a result of their exposure to use during the Six Day War in 1967.

Migration from traditional cannabis using countries to countries where cannabis use has not been entrenched has been cited as a factor in its spread. Israel reports that this is true for many of the migrants coming from Middle Eastern and North African cultures, England cites this for its Asian and African migrants, and it is probably also true of France, with many people returning to the mother country from the Middle East or from her former African colonies.

In some countries (parts of South Africa), the Caribbean, cannabis use is the direct result of the introduction of the plant by East Indian migrants.

What all of the above methods of diffusion of the plant have in common is the fact that the methods of social control common in the countries of origin (with centuries of use) are no longer operative. In addition, one has to consider in countries with a strong Moslem tradition, the relative availability of an alternative intoxicant, alcohol, as well as its comparative cost.

There is little information available on the methods of introduction to the use of the plant (by peers or by an older user, by family members or outsiders, or the number of persons who either abandon the effort to find usage attractive after the first few attempts, those who persist as occasional users, those who incorporate cannabis use as a major feature of their life style). Present reports from Western countries indicate that the occasional user is typical in America and Europe, while in Near Eastern countries heavy users predominate.

What we know of alcohol use in our own country would seem to indicate a wide pattern of diversity of use. (It is instructive to remember that nationwide studies in this area are very recent - only within the last ten years.) Studies of the use of psychotropic drugs in the general population (drugs employed for many of the same reasons that cannabis is used) are even more recent.

There is a great need for good cross-cultural studies to look into many of the phenomena mentioned above, but they are exceedingly difficult to mount. In many of the countries where cannabis use is a centuries old phenomena, there is a shortage of trained epidemiologists and social scientists in general - yet any adequate account of cannabis use must take into account the cultural matrix in which it is embedded. Unfortunately, in many of the

industrialized Western countries where cannabis use has been seen as a growing problem, some scientists (usually physical) have sought to translate their own interest in one aspect of cannabis use, and their own research techniques, to another setting in another country, with little or no effort to investigate anything but the most obvious (employment and criminal records) socio-cultural concomitants of use.

English Speaking Countries

Within the past four years, notable reports on cannabis have been published in Great Britain, Canada, Australia, and New Zealand. Each of these reports drew on a variety of professional disciplines during the compilation, and each of the Commissions charged with the duty of writing the report sought testimony from citizens (non-professional) to determine something of the public temper regarding the drug.

England

There are at present no published surveys similar to the national household survey in Canada, or the national survey in the United States published by the Marihuana Commission. There is, in addition, no large scale survey data available on use by secondary or university students. A number of small scale studies indicates, however, that the introductory drug for many high school students seems to be some variety of stimulant. These drugs, since they can apparently be gotten from the parental medicine chests, are cheaper than hashish or marihuana, to which young people graduate about the time they are either earning their own money or have achieved a higher allowance when they enter the universities. England, however, has never had a widespread outbreak of stimulant abuse, such as that suffered by Sweden. There is indication in literature (novels, short stories, etc.) that the course of cannabis use in England has been closely parallel to that in the United States and Canada - initial use by an avant-garde intellectual or artistic elite with ritual and/or mystic overtones, and then with diffusion to other social classes, a differential use pattern. The picture in England, however, must differ to some extent from that of the United States and Canada, because of the tremendous migration in the last few years of British nationals from traditional cannabis using countries to the mother country.

Australia and New Zealand

As we indicated in last year's report, Australia and New Zealand is an area where the use of narcotics, marihuana, and stimulants is relatively uncommon. There was little if any use of intoxicating substances by the pre-European indigenous people; there has been comparatively little migration to either of these countries by people from countries where the use of cannabis was well entrenched. Alcohol use, on the other hand, in both countries, continues to be a major problem.

In the 1971 report we summarized the findings (1970) of a special committee, set up under the Board of Health, to report on Drug Dependency and Drug Abuse in New Zealand The committee indicated, at that time, that they were not prepared to give a complete picture of cannabis use in New Zealand, but believed that several groups could be identified - multiple drug users (combination of cannabis and other drug use), and the cannabis only users, who could be split into experimental and occasional or spree users. Reports available to the Commission at the time of the publication of the report indicate that in New Zealand, as in England, the drug of initiation is not usually cannabis.

To our knowledge there have been no nationwide studies of the use of cannabis or other drugs in New Zealand, or even specialized studies of the use of cannabis by university or secondary school students. There is always a publication lag, however, in addition to the explosion of articles having to do with cannabis. The Canadian report suggests that some sort of an International Documentation Center be set up to insure not only that researchers in various countries be kept abreast of studies being carried on, but also to insure that there not be duplication of effort.

Australia

In 1969 a special Select Committee of the Senate, consisting of eight members, was appointed to look into the problem of drug abuse in Australia, with wide terms of reference. This committee did not contain as many medical members as similar committees have in England, or Canada, so there is not so much emphasis on pharmacology as there is on the problem of people (5) as the Senate members themselves report.

The report to the Senate was made in 1971. Commission members found that the drugs most widely used and abused in Australia, in order of frequency, are alcohol and tobacco, barbiturates, bromides and other sedatives, minor analgesics, cannabis, amphetamines, opiates, LSD. Although there are no fully reliable statistics, the evidence points to the fact that cannabis, mainly in the form of marihuana, is the illicit drug most widely used.

Cannabis use has spread through all sections of society from young experimenters to professional groups, but there is as yet little evidence that there is extensive use among older age groups. The committee found that, according to present evidence marihuana is not so dangerous a drug as might have been previously believed; however, they state that scientific evidence is not yet sufficiently conclusive to warrant the removal of existing restrictions on the use of any of the cannabis derivatives.

They recommended that the Australian government initiate action for the transfer of cannabis and its derivatives from Schedule I of the 1961 Single Convention on Narcotic Drugs to an appropriate schedule in the Convention on Psychotropic Substances. They also recommended that cannabis research should be encouraged, but specified the following conditions:

1. Unless specifically original research, these efforts should be channelled into complementing overseas research instead of duplicating it.

2. Priority should be given to research complementary to investigations being undertaken in the United States and that projects be arranged under the existing Australian-American Scientific and Technical Cooperation Agreement.

3. Sociological research should be encouraged as a matter of urgency in Australia by Australian organizations.

4. Legislation should provide adequate protection in law for those taking part in approved cannabis projects.

5. The allocation of funds for medical research should be the function of the National Health and Medical Research Council.

The Committee further recommended that urgent action (5) be taken by the Commonwealth Department of Health with the cooperation of State Departments of Health to organize, survey and assemble statistics on all forms of drug abuse on a uniform basis throughout Australia and that such information be made available freely to research and other interested organizations.

Funds, separate from those already allocated to the National Health and Medical Research Council for general medical research, should be provided by the Commonwealth Government for the stimulation and conduct of research into drug abuse in Australia. Consideration should be given to the appointment of a Director of Social Medicine either as part of the Commonwealth Department of Health or as the leader of a separate institute whose role would be to serve as focal point for the coordination of all activities into medical, education, and statistical research related to drug abuse in Australia.

The Committee found that existing education programs aimed at correcting drug abuse are inadequate. (5) They recommended that no program directed against drug abuse in isolation be undertaken since they felt that, almost by definition, it would be ineffective. Instead, commission members suggested that education programs in schools be designed as "education for living" as the best long-term preventive measures.

They recommended that one national group, a National Education Council representative of the Commonwealth and all the States, with membership drawn from a variety of disciplines (including education, medicine, social health, the legal profession, social workers and youth leaders) be set up to supervise all education programs. This Council would be charged with the duty of 1) developing specially planned programs designed to meet the needs of differing age groups; 2) undertaking curriculum research to establish guidelines for new school programs in all States and Territories of the Commonwealth; 3) develop programs for the training of teachers and counselors; 4) support programs, including seminars directed specifically to the adult population; 5) serve as a National Resource Center for the collection and dissemination of factual information.

The Senate Committee, in the course of hearings conducted throughout the Commonwealth, found that there was strong evidence of the need for psychiatric and counseling services among children, and recommended progressive development of these resources with the central government contributing financial support. They further suggested that in any proposals for the extension of child care centers it should be ensured that full advantage be taken of all available research knowledge.

One of the most important recommendations of the Senate Committee, and one fully in accord with their emphasis on the human rather than the pharmacological aspects of drug use, was one concerned with the living environment. (5) "The priority being placed on the growth, development and material wealth should be critically examined so that greater resources may be devoted to improving the living environment of the community."

Canada

In 1972, the Commission of Inquiry into the Non-Medical Use of Drugs published their report on Cannabis. An Interim Report had been published, and at least one more summary volume, dealing with multiple drug use, will be forthcoming. The Cannabis report deals with the nature and effects of cannabis, its distribution, patterns and extent of use. The Commission also examines the existing laws concerning cannabis, and makes recommendations to the Federal Government concerning legislative policy. In other words, the Canadian report encompasses, in one study, the types of material from the United States which must be searched for in two studies - the annual Marihuana and Health Report from the Department of Health, Education, and Welfare, and Marihuana, A Signal of Misunderstanding, emanating from the Marihuana Commission (a specially appointed body).

To place this report in proper perspective it is necessary to recall the Commission's terms of reference, set forth in the Order-in-Council (P.C. 1969 - 1112) which established the Commission on May 29, 1969.

(a) to marshal from available sources, both in Canada and abroad, data and information comprising the present fund of knowledge concerning the non-medical use of sedative, stimulant, tranquilizing, hallucinogenic and other psychotropic drugs or substances;

(b) to report on the current state of medical knowledge respecting the effect of the drugs and substances referred to in (a);

(c) to inquire into and report on the motivation underlying the non-medical use referred to in (a);

(d) to inquire into and report on the social, economic, educational and philosophical factors relating to the use for non-medical purposes of the drugs and substances referred to in (a) and in particular, on the extent of the phenomenon, the social factors that have led to it, the age groups involved, and problems of communication; and

(e) to inquire into and recommend with respect to the ways or means by which the Federal Government can act, alone or in its relations with Government at other levels, in the reduction of the dimensions of the problems involved in such use. (4)

To carry out its work the Commission held a series of public hearings, undertook a series of special research studies, sought advice and consultation from experts drawn from a variety of disciplines, both inside and outside the country.

The Commission points out that they relied to a significant degree on research in the social sciences to amplify their knowledge and understanding of cannabis use. (4)

The Commission held public hearings for 46 days, visiting 27 cities and 23 university campuses in all provinces of the country. Members estimate that approximately 12,000 persons attended these hearings, and they feel that they provided the means by which the Commissioners could get a feeling of the response of the public to non-medical drug use.

The Commission initiated several national surveys to determine the extent and patterns of use of cannabis and other drugs, studied the use of cannabis and other drugs by young people using participant observer techniques. It conducted a formal survey of psychiatric hospitals, a study of physicians practicing in the Ottawa area and an investigation of innovative service and street clinics, as well as some formal treatment facilities in various parts of the country. The Commission also conducted a study (one of the very few in existence) of the social and personal characteristics of Canadians over 27 who were conventionally employed and also users of cannabis.

To determine the legal and economic implications of cannabis use, the Commission initiated a study to determine the sources and distribution networks involved, as well as detailed empirical assessment of the existing law and law enforcement methods.

The Commission conducted three systematic national surveys in 1970 of high school students, university students, and the rest of the population. These were the first such national surveys which had been conducted. The samples of these populations are as follows:

(1) High school students from the ages of 12 to 19 years, enrolled in grades 7 to 12 or 13. These students were interviewed in homes selected for the National Household Survey, described in (3) below. More than 1,200 students were interviewed in this survey.

(2) A total of 1,213 students attending colleges and universities in Canada at either the undergraduate or graduate level. Each student selected for this survey was provided with a letter explaining the study, a copy of the questionnaire and material for return mailing. The students selected were from 8 large and 12 smaller institutions representing all regions of the country.

(3) Some 2,800 households, in which an individual in each household was interviewed under a method of selection that ensured an equal opportunity to be interviewed for each member of the household 12 years of age or older who was not attending a primary or secondary school. (4)

The Commission of course also had the results of previous partial surveys which had been made of high school and university students. Although final analysis of the data collected in these various surveys has not yet been completed, enough analysis has been done to show that there has been a very rapid and sharp increase in cannabis use in Canada within the past five years. On the East Coast hashish is the drug most in use apparently because of its greater availability, but on the West Coast, because of proximity to Mexico, marihuana is still the drug of choice.

According to their surveys an estimated 79,000 persons had begun to use cannabis by 1966. By 1970 an estimated 850,000 persons had used it at least once. By mid-1971 it is estimated that as many as 1,500,000 had done so. The surveys indicate that a significantly large number of persons who have used cannabis have used it only on an experimental basis (two or three times). Continuing analysis of the survey data will allow estimation of the number of experimenters who have graduated to occasional or frequent use.

During the mid-sixties cannabis use was concentrated on college campuses, and university students continue to have a higher incidence of use than any other segment of the population. Apparently, the proportion of university students who are users is still rising. In Canada, as in the United States and other countries, the extreme differences between users and nonusers, such as the "hang-loose ethic" found by Suchman in 1967 no longer apply. The users and nonusers can still be distinguished along some societal variables, but it is likely that even these distinctions will eventually be eliminated if the present trend towards greater use and acceptance continues.

An ever increasing number of high school students are being introduced to the drug while in their early teens, and the distinctions between users and nonusers is becoming more blurred in that group as well. There are no surveys of drug use among grammar school students in Canada.

The general population national survey indicated that by April 1970 approximately 3.4 percent of the population had used cannabis (about half a million persons). The accumulated evidence to date indicates that it is primarily a middle and upper class phenomenon found among those in their twenties and thirties.

The Commission used anthropological (primarily participant observer) techniques to study those persons whose highly mobile life styles generally insure that they are missed in more conventional surveys. Because of the lack of any surveys and the constantly changing dimensions of the population, it is difficult to give any reliable estimate of the number of so-called "street people," but there is no doubt that the number in Canada, as in the United States, has been increasing in the last five years. In addition, in

Canada as in this country there is an increasing number of persons living in communes of various sorts.

In Canada the "street people" range in age from thirteen or fourteen (during the summer months) to the mid-thirties or even older (4), but most are between eighteen and twenty-four with the average age for males being about twenty-one and perhaps slightly lower for females. Males tend to be overrepresented. In the early days of this phenomenon (1967) it was primarily middle and upper class youngsters who were attracted to the street scene, but now there is increasing evidence that more and more poorly educated young people drawn from the working class have become street people. The influx of working class youth, as well as an attenuation in the attraction of the Flower Children myth has led to a decline in the number of middle and upper class youths who are found in these favored enclaves, but the overall number continues to rise as the number of facilities (free clinics, hostels, drop-in centers) developed to serve the special needs of this population increase.

Each Canadian city, as each American city, has at least one and perhaps more, favored areas - in Vancouver, "Chemical Row" in Kitsilano and Gastown; in Toronto, Yorkville; in Ottawa, the very center of the city along a public shopping mall and the grounds of the National Arts Center.

In Montreal street people are linguistically, culturally, and ecologically divided. French-speaking persons tend to congregate near the Carre St. Louis and old Montreal, and English-speaking young persons favor an area (known as the Ghetto) just east of McGill University, and another section quite close to Sir George Williams University.

The daily smoking of cannabis or hashish is more the rule than the exception among street people, and there are no mystic qualities associated with the drug or the purposes for which it is used. Just as in the United States, many of the hard drug users are recruited from the ranks of the street people.

However, most cannabis users do not end up in the street populations. The Commission, in an attempt to tighten up the ill-defined boundaries concerned with levels of cannabis use, came up with three categories. The first level of continued consumption (beyond initial experimentation) was called occasional use (defined as once a month use or less). (4) More cannabis users studied by the Commission fell into this category than any other.

Occasional use characterized 29 percent of secondary school users, 39 percent of university users, and 46 percent of those interviewed in the national survey. It is, of course, impossible at this juncture to predict how many will give up cannabis altogether, and how many will advance to more extensive use. For the occasional user, cannabis is a pleasant diversion and is not viewed as occupying a prominent place in his life, is not pursued to the extent that he feels it necessary to be in touch with a regular dealer.

The moderate-regular users, for the purposes of the Commission, were defined as those who use cannabis more than once a month but not more than once a week. Nearly 29 percent of secondary school students, and 22 percent of

university students fall into this category. It is, of course, necessary for these users to have a regular supply of the drug. In general, however, their drug taking is confined to occasions when it will not interfere with other activities. Use usually takes place in a recreational context.

The third pattern of consumption of cannabis is heavy-regular use - for the purposes of the Canadian survey defined as all those who regularly smoke cannabis from more than twice a week to several times each day. Only 6 percent of the cannabis using university and secondary school students used the drug as frequently as several times a week, and an additional 1 percent of the high school students and 3 percent of the university students claimed that they smoked every day. This is the pattern of consumption that is found in many non-Western communities, but it is relatively rare in a North American sample to find this heavy consumption pattern, and even rarer to find a cannabis only consumption pattern.

The Commission points out that they did not collect data on a systematic national basis on the relative potency of cannabis used in Canada. (4) Although the existing data shows that cannabis is not usually adulterated with other active drugs, it is sometimes cut with inactive materials. The report suggests that continuing qualitative and quantitative analysis of randomly selected samples from police seizures, as well as samples procured from other sources, would be a suitable method of monitoring the purity and potency of cannabis used in Canada. This kind of data, of course, should be supplemented with material from other countries. Unless and until there is a sizable body of such information available, cross-country comparisons will be exceedingly difficult to make.

They point out that in the past almost all research has been conducted on healthy young adult males. (4) The time has come to investigate other populations, adolescents, females, and older persons of both sexes. It is noteworthy that the Commission itself moved to remedy this deficit by using females in one of their experiments (the third phase of their continuing study of chronic cannabis use).

The Commission members also suggest that further attention be directed to the possible effect of cannabis on muscle strength and work performance by measuring, under both laboratory and natural conditions, the effects of acute and chronic cannabis use. (4) The existing literature in the field is far from conclusive although some deficit is suggested. Since cannabis is used as a work adjunct or as a stimulus in so many countries of the world, this kind of research would be very valuable.

The Commission recommended (4):

> The Federal Government should remove cannabis from the Narcotic Control Act, as the Commission recommended in its Interim Report.
>
> The Federal Government should immediately initiate discussion with the provincial governments to have the sale and use of cannabis placed under controls similar to those governing the sale and use

of alcohol, including legal prohibition of unauthorized distribution and analogous age restrictions. Furthermore, this government-distributed cannabis should be marketed at a quality and price that would make the 'black market' sale of the drug an impractical enterprise.

The Federal Government should initiate a program to develop efficient practical methods for cannabis production and marketing in Canada. A standard form of natural marihuana would seem to be most feasible at this stage, but hashish and synthetic preparations should also be explored.

The Federal Government should initiate prospective multi-disciplinary epidemiological research to monitor and evaluate changes in the extent and patterns of the use of cannabis and other drugs, and to explore possible consequences to health, and personal and social behaviour, resulting from the controlled legal distribution of cannabis.

All stages of the production and marketing of cannabis should be conducted by the Federal and/or provincial governments.

One commissioner, Ian L. Campbell dissented, "I must dissent from the recommendation of the majority of my colleagues and recommend that the prohibition on the possession of cannabis be maintained, for the time being at least. Possession of cannabis should be punishable, upon summary conviction, by a fine of $25.00 for the first offence and by a fine of $100.00 for any subsequent offence."

"With respect to the cultivation of cannabis other than for purposes of trafficking, I recommend that it continue to be an offence with penalties identical to those which I recommend for simple possession." (4)

Europe

The bulk of the cannabis use in Europe is in the form of hashish, a more potent form than the marihuana of the United States. Some Western European countries became concerned about drug use among juveniles much earlier (1967) than did the Eastern European nations, if national surveys about drug use provide a valid indication of concern. Moreover, there is a difference between countries in the type of drug which first triggered their concern, and the country's concern with, and knowledge of the use of a legal drug, alcohol.

For example, Sweden has been aware of the problems of alcoholism for at least a century and a half, and was one of the first countries of the Western world to deal with the problem of what amounted to almost an epidemic of stimulant drug abuse. The first studies which involved monitoring a number of pharmacies to determine the amount of amphetamines dispensed, were published in 1944. As early as 1966 a committee, The Narcotics Drug Committee,

comprised of five subcommittees dealing with such aspects as social medical aspects, methods of prevention, and treatment and legislation, was set up. Sweden has since conducted a series of model epidemiological surveys, not only dealing with drug use among juveniles of all social classes but also keeps a national register of drug abuse cases coming to the attention of hospital authorities (both mental and general hospitals). As early as 1967 Swedish authorities conducted a study of 130,000 pupils in secondary schools, and found that about 3.6 percent of the pupils took, or had taken, "narcotic" drugs. Sweden classifies cannabis among the narcotic drugs. At the time of that early survey about 1,260 pupils had used cannabis. Sweden is still far more concerned about the abuse of amphetamines than it is about the use of cannabis.

It is interesting to note that a neighboring country, Denmark, has not had to contend with the problem of amphetamine abuse to any great extent. Hashish still seems to be the illicit drug of choice. Scientists have conducted a series of surveys in the last four years to determine the drug using habits of adolescents both in and out of the schools. These studies indicate that between 12 to 28 percent of the samples had tried hashish. Only between one and four percent of any sample smoked the drug as often as once a week or more. Findings as to the type of youngsters who experimented with hashish use were similar to those in the United States and Canada, that is, the higher the educational attainments of the father and the mother, the greater the incidence of experimentation. In addition, as the number of experimenters increased the Danish investigators found that it was not possible to distinguish regular users from their nonusing confreres in terms of such demographic variables as sex, age, status, background, or degree of urbanization. For these, and similar reasons, the researchers have concluded that it is not theoretically productive to consider drug use from the point of view of deviancy, but rather from the point of view of social change. Needless to say, the influence of this type of view on the lawmakers and law enforcers could have far-reaching implications.

The Scandinavian countries, and the Netherlands must deal not only with the problems of drug abuse by their own nationals, but also that of the armies of young people (from various countries including the United States) who arrive in the summer months.

Some European countries (for example: Germany, Belgium, France) within the last ten years have witnessed an unprecedented influx of workers or migrants from countries where hashish and/or opium use has long been a culturally accepted fact of life. Germany, in particular, has ranged far afield to find workers for her expanding economy. While many of these have been recruited from within neighboring European countries, many of them have also come from the Middle East. Belgium also employs many Middle Eastern nationals. France, at the close of the Algerian war, accepted thousands of settlers (French citizens) who came from North Africa. Although there is little documented information to indicate the extent to which some of these immigrants have been involved in the increasing social acceptance of hashish, there is a considerable amount to show that a few of them have had a definite role to play in getting the preferred drug to the market.

It is extremely difficult (some would say almost impossible) to get a clear assessment of the social climate of any country, the massive attempts (not yet very successful) to develop social indicators in the United States, are a clear indication of that. However, it is increasingly clear that in the developed, industrialized nations, as well as the so-called underdeveloped nations (where the cannabis habit has had the longest history) any really thoroughgoing study of drug use (of which cannabis is only a part) will have to take into account the diversity of population groups represented, the amount of drug use, legal and illegal, prescription and over the counter drug use. Moreover, the general mind set of the country will also have to be considered.

It is no accident, for example, that the Netherlands, with a fairly liberal policy to deal with drug use, is also the country which is in the forefront of liberal Catholicism. The general attitudes towards health and illness (including physical and mental) and the favored methods to either maintain health (avoid illness, attain a state of emotional well-being) or to regain health, all play a part in the use of drugs.

It would seem, finally, that the time is long overdue to initiate a comparative study not only on drug use per se, but on the methods of dealing with it. No one pretends that there is sufficient data available in any one country to undertake a thoroughgoing systems analysis, and of course the problem is magnified a hundred times if one attempts a cross national survey. Still a start could be made (there could be a central depository) which could contain data on the volume of psychotropic drug prescriptions, as well as the prescribing practices of medical doctors and psychiatrists in several countries. This could be coupled with general data on health (morbidity, mortality). The school systems could be asked to furnish data on health education classes (if any) carried on. The number of examples could of course be multiplied many times over. At present, the kinds of data we are speaking of may be available, but the potential researcher must search for it in too many places and must consult too many government bureaus to make it worthwhile. Still, it would seem reasonable to muster a major amount of research effort to attempt to get an overall picture which is as comprehensive as possible.

The Netherlands

In 1968, in order to supply some hard data about the extent of drug-taking in the Netherlands, a series of studies was undertaken by Buikhuisen and Timmerman of the Criminological Institute of Groningen University. These studies included: 1. an investigation of drug-taking and drug policy at youth centers; 2. a survey of the extent of drug-taking among secondary school children, of the sociological and psychological characteristics of those children who take drugs, and a field study in depth of drug-taking in a small provincial town. The investigators have carried out two studies, one in 1969 and one in 1971, of the drug-taking habits of secondary school children, and they plan a third survey in 1973.

In the first survey in 1969, 11,659 students in 156 schools, scattered throughout the Netherlands, answered the questionnaires. Data collected included standard demographic material such as sex, age, father's occupation, type of course being taken and certain particulars on the use of drugs. Of the children queried, 1,300, or a little over 11 percent, said they had taken one or another drug at least once. Hashish and marihuana were by far the most popular drugs and 88.3 percent of the users had taken them. The proportion of students who had taken the cannabis drugs in addition to others such as amphetamines, LSD and the opiates was comparatively small; amphetamines were taken by 13.7 percent and LSD by 12.3 percent of the users, while the opiates were taken by only 7.2 percent of the students.

There was a difference in magnitude of drug use according to the type of school. It was highest at schools of the arts - almost 30 percent, little over 15 percent at secondary schools, and almost 9 percent at technical schools. Moreover, there is no difference by age groups in the drug and non-drug users at the arts schools, but at the other two types of schools, the drug-takers tended to be older. In all types of schools, the proportion of drug-takers is higher among boys than among girls. Relatively more of the drug-takers belong to the upper social class than to the middle class. (It should be borne in mind that class differences are not nearly so marked in the Netherlands as they are in larger countries.)

The investigators repeated this survey in 1971, and a total of 17,708 children in 32 towns were studied. By this time the percentage of school children who have taken drugs at some time or another had advanced to slightly over 20 percent and those who had taken drugs more than 20 times had gone from a little over 2 percent to 6 percent. The type of drug favored was still marihuana or hashish. The differences found in 1969 in regard to social class and age had disappeared by 1971. Only the sex variable was still a factor.

The researchers believe, on the close examination of their data, that drug-taking is already reaching a saturation point in the Netherlands. The expected near doubling in the number of drug-taking children in all schools has not occurred. In those schools in which the rate was high in 1969, the increase in 1971 was small - most of the increase represented diffusion to new schools. The overall frequency remained comparatively low, although there was an increase in the number of girls using drugs.

The Near and Middle East

In previous reports we have commented on the extensive literature available on cannabis use in countries in this section of the world where cannabis (primarily in the form of hashish) has long been employed, and have stressed the extreme caution with which these reports must be viewed. It is in good part from these countries that Europeans acquired their knowledge of the "good" and "evil" qualities of the drug. In this report, we summarize the results of an extensive study of hashish use in a Near Eastern population - that of Soueif in Egypt.

Egypt

Egypt was one of the first countries (1879) to ban the use of hashish, even though at that time there was very little cannabis under cultivation. Illegal hashish immediately began to pour into the country from Greece, Lebanon, and Syria. Today the latter two countries are still seen as the major suppliers of the market.

Since 1879 (10) successive laws have shown a persistent tendency to enforce more and more severe penalties on traffickers and users, which presumably shows that the problem of use has been growing. There is also some indication that the absolute amount of hashish used has been increasing in the country in the years since the close of World War II. However, the enforcement officials seem to have been able to keep the supply of narcotic drugs including opium, heroin, and cocaine at about the same levels during this period.

Although there are no exact figures on the number of hashish users in Egypt, Soueif (the leading researcher in the field) estimated in 1967 that there were approximately 180,000 users, the majority of them young men between the ages of 20 and 40. The estimated number of young men in that group out of the entire population of Egypt was about 3,000,000.

In 1957 Dr. M. Soueif of Cairo University undertook a series of far-reaching studies of hashish users which give by far the most complete data available for all of the Middle East. The investigators began by constructing a schedule of questions which were derived not only from suggestions made by psychiatrists, psychologists, and workers in related fields, but also through voluntary interviews (obtained through contact men) with hashish users themselves.

Demographic data was collected on age, education, monthly income, marital status and other related items, but the interview schedule was also designed to elicit information on the following topics:

1. Personal estimation of the distribution of hashish use in different sectors of the society.

2. The effects of hashish use as experienced by the interviewee.

3. The sexual behavior of the interviewee.

4. Hashish effect on appetite for food, drink, and general energy output.

5. Perception and thought, emotional set, self-image.

6. Interviewee's opinion regarding the increasing severity of the successive legislation regarding hashish consumption and trafficking.

7. Any evidence of cumulative effects of the habit.

8. Work and recreation.

9. Description of group use "hashish party".

10. Extensive data both on family of origin and of procreation, with particular attention paid to history, if any, of pattern of hashish use within the family.

The interview schedule for the controls was identical; only those items concerning first-hand experience with the drug were eliminated. After a series of trials it was decided to word the questions in colloquial Arabic which proved comprehensible both to literate and illiterate subjects.

Interviewers were required to have at least a bachelor's degree in psychology and in addition were screened to be sure that they were adaptable, interested in the work at hand, and above average in intelligence. Each interviewer was trained for three months before starting the job; not only were they thoroughly grounded in the methodology involved in the construction and administration of the schedule and the method to be followed in recording different types of answers to different types of questions, they also observed the interviewing process of senior interviewers. In addition, they conducted a series of interviews under the direction of experienced staff members.

In 1967 Soueif reported on the first group of studies done with two groups of users, one recruited from Cairo, the other from semi-urban and rural parts of upper Egypt. Hashish use was defined as at least once a month in the year preceding the time of the interview. Two studies were done with control groups - a control was defined as one who had never had the experience of taking hashish. All interviewees were volunteers, and all were paid. In this first series of studies no prisoners or mental hospital patients were included. The investigators do not state that the groups represent a truly random sample since users were located through the use of a key informant and then so-called snow-balling technique, a method it should be recalled which has been extensively used in United States studies.

The hashish users from Cairo constituted a group of 204, ranging in age between 20 and 52 with a modal age of about twenty-two and a half years. Thirty subjects were illiterate, 43 semi-literate, 110 had had from 4 to 9 years of formal schooling and 20 were university graduates. There was a roughly even distribution between the married and the unmarried. Most of the subjects were Moslem.

The group of rural users comprised 49 subjects ranging in age from 20 to 47 years with a modal age of about 20. Fourteen of these subjects were illiterate, 15 semi-literate, 13 had completed 4 to 9 years of formal schooling and only one was a university graduate. The majority of the subjects were married. All subjects were Moslem.

The favorite method of consumption for both groups (urban and rural) was smoking with a "josah." This is somewhat similar to the pipe nargileh used in Lebanon. The second most favored method of consumption is through smoking of hashish cigarettes. There is no information given in the published material as to the amount of tobacco, if any, mixed with the hashish. Most hashish was consumed in a group setting.

The modal frequency of hashish use for the urban group was about 12 times a month, with the upper 10 percent of the sample exceeding 50 times per month. The modal frequency for the rural group was about 8 times per month. About 70 percent of the subjects in the urban group had begun to take hashish before the age of 20, and the corresponding proportion for the rural group was 62 percent. Very few of the subjects began use after the age of 28.

The main motives for starting to take the drug in both urban and rural groups are (in descending order of frequency): Conformity to group norms, desire for euphoria, curiosity, and the desire to appear like "real men." It is a little difficult, from the published material, to determine what is included in the concept "real men." It was a separate category, distinguished from "sexual behavior." Incidentally, enhancement of sexual performance or enjoyment came rather far down on the list of desirable attributes associated with the taking of the drug.

One of the most interesting findings of this study, and one which differs fairly sharply from findings in the Western World, was that concerning the makeup of the group in the group setting favored by an overwhelming majority of the users for consumption. All members of these groups seemed to feel a sense of social nearness, although more often than not, they belonged to various occupational categories and sometimes came from different socio-economic strata. Much of the cohesiveness of the groups in both the rural and urban settings seems to depend on the characteristics of the leader. The leader should be a man who is modest, an organizer and a fluent conversationalist, according to those interviewed.

The two control groups (about 115 in the urban sample and 40 in the rural sample) were matched on all relevant variables. They were defined, it will be recalled, as persons who had never taken hashish. Unfortunately, the published data does not tell us why they had never used hashish since presumably they would have been exposed to the drug with about the same frequency as the users. Also, the definition of a control excludes persons who might have tried the drug once or twice and then abandoned it either because they found the drug physically or mentally upsetting, or because of fear of arrest.

Late in 1971, Dr. Soueif reported on a large study undertaken with prisoners (both users and nonusers of hashish). The experimental group (850) included the entire male population convicted exclusively for use of hashish and detained in Egyptian prisons from June 1967 through March 1968. Ages ranged from 15 to slightly over 50, with an average age of 39. Subjects were drawn both from urban (460) and rural prisons (390). The majority (50 percent) of subjects were illiterate, about 25 percent of the group were skilled laborers and the rest had held a variety of unskilled jobs.

Controls (defined as those who never took hashish or any other narcotic substance, as defined by Egyptian law) were selected from among a group of convicts in the same prisons where the experimental users were confined. To reach controls the investigators depended on key men and preliminary screening interviews. The control group is fairly well matched to the experimental

group regarding age, urban or rural background, and percentage of skilled laborers. There were fewer illiterates (roughly 55 percent among the controls) and the control group also included 44 subjects with high school certificates and 9 university graduates.

In addition to the interviewing items which had been included in the earlier surveys, the investigators also included a series of twelve psychological tests, in order to examine a series of hypotheses developed during the earlier surveys. It is noteworthy that the researchers decided that the tests to be used should meet certain criteria (to be widely known among Egyptian psychologists and those in other countries and to be as culture free as possible) so that they could serve to make possible future comparisons across researchers and across cultures.

Both interviewing and psychological testing was designed to be accomplished in one session, and tests were administered (in random order) at the end of the session. Interview and testing were carried out in a private testing room.

The psychological tests included Tool matching, H marking, Speed testing, Mark making, all taken from the General Aptitude Test Battery. There was also one test (Trail Marking - Part A) taken from the Reitan Battery, the Bender Gestalt, Digits Forward and Backward from the Weschler Adult Intelligence Scale, and an initial reaction time test which utilized four Rorschach cards, and timed the verbal response of the subjects in seconds from the time of the presentation of the cards.

The prison study found that smoking continued to be the preferred method of administration (almost 90 percent). Smoking as a preferred method of administration was slightly related to the number of times per month the subject used the drug - 87 percent of heavy users (defined as those who take the drug more than 30 times a month) preferred smoking as opposed to 93 percent of the moderates (those who take the drug 30 times or less). More heavy than moderate smokers tended to take the drug at definite hours of the day. Almost all drug users prefer (94.2 percent) to take the drug in the evening, and in groups of four to six members (82.5 percent). Only about 17 percent of users take hashish on their own and heavy users do not differ from moderate users in this respect. However, city dwellers have a significantly higher proportion of lone users than do rural inhabitants.

The frequency of hashish use was significantly related to the time of the beginning of the habit; for example, 76 percent of those who started drug use before 22 were heavy users, as opposed to only 56 percent of those who started after 22.

Some of the hashish users also took other drugs known to act on the central nervous system. Almost one third of the group admitted that they also used opium, and almost 23 percent also used alcohol. Unfortunately, there is no indication in the printed work of exactly how much opium or alcohol the subjects used.

Motivation for use in the prison population did not differ much from the non-institutionalized samples studied in the first group. (In rank order these reasons for use include conformity to group expectations, seeking euphoria, acting like real men, and so on.) It should be borne in mind that the prison group differed markedly from the subjects in the first study, where the modal amount of urban use was about 12 times a month. In the prison study about 70 percent of the users take hashish more than 30 times a month.

In regard to cannabis use, the investigators found that attempts to interrupt the habit as well as the frequency of drug use were related to age at onset; the earlier the age of onset, the fewer the attempts at interruption and the higher the frequency of drug taking. In addition, the investigators established a positive relationship between duration of hashish use and opium taking. (Unfortunately, the results published so far do not indicate whether opium and hashish were mixed or whether opium was used alone.)

By comparison with controls, cannabis users have had fewer criminal offences (other than those directly connected with using or selling narcotics). Cannabis users are, in general, slower learners than the controls. In addition, the differences between users and controls were accentuated when considered in light of their educational attainments; the higher the educational attainments, the larger the discrepancies between users and controls on the objective tests.

The final results of the prison study still have not been published. It is to be hoped that future work will take into account the possible confounding effect of opium and alcohol use as it relates to the test performance of the hashish users.

Latin America

Cannabis is not indigenous to the New World. The cultivation of hemp was apparently introduced into North America by Champlain's apothecary in 1606, in the territory of Nova Scotia. Shortly thereafter, the Pilgrims planted hemp in New England. Both France and England encouraged the cultivation of hemp in their colonies both for domestic requirements such as clothing and cordage, and to provide sails and rigging for their ships. Later, this encouragement was supplanted by regulations requiring the growing of hemp (for example, in Virginia), and fines were imposed on those who refused to comply. There were suggestions made in New Spain (Mexico) as early as the first century after the Conquest, that hemp be introduced as a major crop.

The varieties of cannabis which might be utilized for medical, religious, work adjunct, or recreational purposes were also unknown in the New World. There is no mention of the plant in North American Indian medicine, or in early studies made of native hallucinogenic or medicinal plants in countries conquered by the Spaniards, including Mexico, the Central and South American countries (except Brazil) and many of the Caribbean islands. The cannabis plant is not represented in any pre-Conquest sculpture or painting (although many other hallucinogenic plants are).

What was in existence, however, particularly in that part of North America now belonging to the United States, as well as in Mexico, Central America, and all of South America, was not only a tremendous store of other narcotic and hallucinogenic plants, but also a culture which would encourage their use. Schultes, for example, points out that the New World cultures have employed many more species of plants hallucinogenically than have the Old World cultures. The reason cannot be botanical, for there is no evidence to suggest that the flora of the Eastern hemisphere are poorer (or richer) in plants possessing hallucinogenic compounds than those of the Western hemisphere. Weston La Barre has suggested that one reason for this curious disparity may be that the American Indians (both North and South) basically preserved as their religion the shamanistic ideology of ancient hunting peoples, with a necessity for a direct psychic experience of the forces of nature, in order to divine their purpose, to try to enlist their aid, or at least avoid their enmity. La Barre believes that substantial portions of this shamanism survived even in societies that turned to sedentary agriculture. In the Old World, however, these plants became less and less important as the old shamanistic religions were supplanted and suppressed by new religions adapted to the demands of agricultural and feudal society. Medieval concerns with devils and witches show some carryover in the belief of sacred and/or magic plants. There are other survival traces in fairy tales and folklore of the magical effect of certain plants.

It should be borne in mind that use of a plant in religious ritual, particularly in underdeveloped regions of the world, by primitive peasants, cannot easily be separated from use of the plant as a direct medicinal tool. Many of the religious rituals are concerned either with divination of a particular illness, mental or physical, or curing of an illness. Since life for many Indians in Latin American countries is indeed nasty, poor, brutish, and short, it should not be surprising that they would also cherish any plant which would help in their work, relieve them of fatigue, or serve to allay the pangs of hunger.

In view of the above considerations, it should be borne in mind that any studies of the use of cannabis in Latin America must first of all differentiate the various patterns of use by varying populations. Studies in the countries with a heavy Indian population (for example, Mexico, Ecuador, Colombia, Bolivia, Peru) would be expected to have a different pattern of use than say a country like Chile, or Argentina, where there is a comparatively small Indian population.

In Mexico, we cite two examples of the ritual adaptation of cannabis in sections of the country well acquainted with other hallucinogenic plants. Undoubtedly, with the growing interest on the part of anthropologists in this field, other instances of the same type will turn up. On the other hand, we should bear in mind that a plant once used ritually (especially by oral consumption) may turn to have more secular-social uses when consumed in another manner, for example, by smoking. That was certainly the fate of cannabis in many Near Eastern countries.

A third caution to be borne in mind is the tremendous urban explosion in many Latin American countries, with hundreds of thousands of peasants streaming into the poor barrios and favelas of all large cities. This type of heavy urban migration has always contributed to the growth of drug use, and moreover drug use which is removed from the social control and sanctions of the rural areas. In last year's report, we listed the countries where there was evidence of increased governmental interest and concern, usually expressed in tightening up of the laws concerning traffic and possession. These countries (preliminary report) included Venezuela, Argentina, Brazil, and Paraguay. The number of countries has increased this year but there is also heartening evidence that equal weight is being given to prevention, education, and treatment.

In Venezuela, the report of the Special Commission Appointed to Study the Drug Problem was submitted to the Chamber of Deputies in June 1972. Although the Commission stated that they believed that the use of drugs was reaching epidemic proportions, they admitted that there was a dearth of reliable statistics. For example, they believe that 85 percent of all young people between the ages of 15 and 25 in the Caracas metropolitan area have used drugs at least once, and that youths of all social classes are involved. Marihuana is stated to be by far the most widely used drug, and most of it is said to come from Colombia. The use of hallucinogens is believed to be limited, but increasing, as is the case with heroin and cocaine. The report did not supply any traffic pattern for these two hard drugs. There is virtually uncontrolled sale and an indication of a growing use of stimulants and depressants.

The Commission recommends that the government and private groups must work simultaneously on three aspects of an anti-drug campaign -- prevention, repression and rehabilitation. They believe that it is necessary to launch a massive educational campaign which will involve training of parents and teachers as well as school children. Rehabilitation facilities are completely inadequate, but there has been a start. This year, for the first time, the government is providing funds for drug rehabilitation.

The recommendations for other funds for drug rehabilitation seem puzzling, especially in view of the fact that the drug most used seems to be cannabis. The Commission comes out strongly against the legalization of cannabis, or any reduction in penalties for use. They do maintain, however, that there should be a distinction in the law between addicts and traffickers, for cannabis and all other drugs.

The Commission recommended that the government (1) take steps to ban the sale of medicine in any place other than a drugstore, and also to require that amphetamines and barbiturates be sold only by prescription; (2) designate a special commission of jurists to study modifications in the penal code and the narcotics law; (3) attempt to establish a community center to deal with adolescent problems; (4) provide drug treatment service in psychiatric hospitals, jails, and prisons.

The Venezuelan report is quite general in nature, acknowledges that much more investigation and study is necessary but the widespread publicity it

has received in leading Maracaibo and Caracas newspapers is an indication of the public interest in the field.

In Ecuador, public concern about drug usage has apparently been aroused through a series of articles in the newspaper "El Comercio of Quito." Based on interviews with Interpol and the Criminal and Security Police, as well as certain educators and other authorities not identified, the newspaper claimed in June that about 600,000 people in Ecuador, about 10 percent of the population, use drugs of one kind or another. Half of the users are said to be in Guayaquil, about one sixth in Quito, with the remaining one third concentrated in other areas of the country, particularly in Esmeraldas, El Oro, and Los Rios.

According to El Comercio, 90 percent of the drug users are males and 80 percent of these are youths between the ages of 15 and 25. Thirty percent of the users are said to be high school or college students, 10 percent university faculty members, and about 55 percent are said to be vagrants or delinquents. About 60 percent of users are said to be lower class with the rest evenly divided between middle and upper class.

There are no reports so far appearing in the literature on indigenous use of cannabis in Ecuador, although there is indigenous use of other hallucinogenic plants.

In July of 1972, the Ecuadorean customs police was reorganized along military lines to help intercept a growing amount of drug shipment across Ecuadorean borders. Enforcement was also stepped up within the cities, and in one evening three cocaine processing laboratories were raided in and near Guayaquil.

The government has announced its intention to ban all "hippies" from Ecuador, although no one is exactly sure what constitutes a "hippy" - a point which has been extensively satirized in the press. It was also announced that airlines flying hippies to Ecuador will be fined, and will be required to remove the offending passengers.

The National Court for Minors has begun a campaign against drug usage by minors. Cooperating agencies include the Ministry of Health, the Ministry of Social Welfare and Labor, and the Ministry of Public Education. One of the initial ideas of this group is to separate minors from other criminals in prisons, which means additional space and hence more money. The National Department of Narcotic Control and Enforcement is planning to give a series of lectures in all middle level schools on the dangers of drug abuse.

There are heartening signs that many of the governments of Latin America are now trying to enlist the aid of specialists in the health and behavioral sciences, as well as from the enforcement ranks, and that, in addition, they are asking U.S. aid in this attempt.

Mexico

Although Mexico is widely known as one of the world's leading producers of marihuana, and the word itself is of Mexican origin, there is comparatively little historical or contemporary socio-cultural material bearing on cannabis use in that country. The lack of historical material is perhaps understandable in view of the fact that marihuana is not indigenous to any New World country. The lack of current material can be explained by the fact that marihuana use was not a widespread phenomenon in Mexico until the last few years.

In contradistinction to marihuana (6), there is extensive documentation, beginning immediately after the Conquest, concerning many of the psychotropic drugs which were used by various indigenous populations in pre-Colombian times and continue to be used. Sahagun (1575-77), for example, described the appearance, place of origin, method of use, and reasons for use of such plants as peyote, ololiuqui (Rivea corymbosa) and teonanacatl ("flesh of the gods"), the hallucinogenic mushrooms. All of these plants were used formally in a sacred context by trained priests or shamans, according to a precise prescribed ritual. Most of the time the drugs were used to communicate with the gods to discover a favored course of action for a community, or to prescribe for members who were ill, or for other divinatory purposes. Even when the drugs were used by those other than shamans, for example, when peyote was used to cure people suffering from fevers, the sacred character of the plants was never lost sight of, and the social control mechanisms militated against their use for simple hedonistic purposes.

Although Sahagun was interested in the entire indigenous herbal medicine armamentarium, he paid particular attention to the drugs which were involved in religious ceremonies because of his desire to substitute Catholicism for the indigenous cults and cult ceremonies. By the beginning of the seventeenth century, writers were beginning to comment on the incorporation of the uses of some of these drugs into Catholic ceremonies. There is no mention of the use of these drugs in the latter part of the seventeenth nor in the eighteenth or nineteenth centuries, but the practice never died out since modern anthropological research has uncovered many sections of the country, and many indigenous groups who continue to use these drugs in much the same way as they were used in pre-Colombian times.

The kind of drug used depends now (as it did before the coming of the Spaniards) on the particular sections of the country and the climatic conditions there. Peyote was used in desert regions, ololiuqui in temperate areas and mushrooms in the humid mountains and woodlands. Use of various types of fermented beverages is common throughout most of the country and causes major problems. This was apparently true even at the time of the Conquest, since the Aztecs provided severe penalties (even including death) for some cases of drunkenness.

In none of the early writings is there any mention of marihuana, in fact, none of the drugs so far described were inhaled. There was, however, extensive use of tobacco in some parts of Mexico especially along the Gulf of Mexico. During the colonial period there is a similar lack of reference to marihuana, and some of the monks recommended during this time that the

cultivation of hemp be introduced into New Spain. In view of the early opposition of the missionaries to the use of mind-altering drugs in non-Christian religious services, it seems certain that the intoxicating properties of cannabis were unknown to them.

No mention of marihuana is found in the proceedings of the Holy Office during the Inquisition, although all of the other narcotic and hallucinogenic drugs are specifically singled out for condemnation. In the exhaustive study of Mexican flora and fauna carried out by Alexander Von Humboldt in the latter part of the nineteenth century, there is no mention of marihuana.

There is no firm historical evidence to support the varying views of when and by whom marihuana was introduced into Mexico. Some persons claim that it was introduced by Negro slaves, and others that it was brought in by sailors from the Philippines to the Port of Acapulco very early in the colonial period.

According to one author, use of marihuana in Mexico came during the regime of Porfirio Diaz and involved primarily prisoners and soldiers. (1) Prisons and barracks were essentially the same because of the Army recruitment system enforced at the time. When a man was found guilty of a minor crime such as robbery or a drunken brawl, he was offered the alternative of going to jail or joining the Army. The country was at peace during this time, so service in the Army involved watching over isolated peasant and tribal groups, as well as service in an auxiliary police force. In fact some authorities think that the word marihuana itself may be derived from the terms Maria and Juan, the latter a derisive term applied to soldiers in general to indicate a lack of individuality (something like GI Joe) and the former Maria to designate their female companions.

Distribution and consumption of the plant spurted upwards about the beginning of the Mexican Revolution in 1910 since the regular Army already included many marihuana users and the revolutionaries adopted it readily. It should be remembered that the Revolution lasted for 18 years and affected almost all regions of the country and all classes of society. The soldiers were transported by train to various assignments and one of the revolutionary songs of the time attests to the popularity not only of marihuana, but also the method of transportation. The song is La Cucaracha. Although it has innumerable verses, each speaking of one aspect or another of the Revolution, it is the recurrent theme which has become the most popular - the cockroach/the cockroach cannot walk, because he's lacking, because he has no marihuana to smoke.

It is probable also that production of marihuana was extended to various parts of the country at that time since the conditions under which it thrives, small secluded valleys with sandy soil, low humidity and a rather cold climate, are characteristic of about 70 percent of the country.

When peace returned, according to most observers, use tended to be once more concentrated among soldiers and criminals, but there is no documentation of this finding. Certainly there is agreement as to the fact that Mexican agricultural laborers, coming into the United States as early as the 1920's, brought their "mota" along with them.

The first cases involving the use of marihuana began to come to the attention of Mexican psychiatrists in the 1930's and in 1937, Dr. Segura Millan published the first and to date the only historical account of cannabis use in Mexico. Such an account, with due heed paid to the interaction of cannabis use patterns with the use of other drugs, both alcohol, native narcotic and hallucinogenic drugs, urgently needs to be written.

Most authorities agree that the early use of cannabis was largely confined to lower socio-economic groups. In addition to the soldiers mentioned earlier, Millan also speaks of miners, lumberjacks, cane cutters, stevedores, and other laborers who perform difficult unpleasant work. By the 1930's use had spread to the urban ghettos of many cities, and the activities of the young unemployed users brought summary attention from the authorities, so that penalties for use and possession were increased. Most of these laws, however, seem to have been enforced primarily in the urban areas, and use in rural areas by specific labor groups seems to have continued undisturbed.

Most observers agree that there are several different patterns of cannabis consumption current at the present time; these include students, the upper classes (of varying ages) in resort areas, Army personnel and prisoners, laborers of various types, indigenous Indian groups who may use cannabis ritually, urban ghetto residents.

There is no doubt of the fact that Mexico is experiencing the first wave of the drug using phenomenon which has long since affected her two neighbors to the North.

Accounts of ritual use of cannabis in Mexico are comparatively scarce, but it may be that further studies will appear in the literature now that anthropological interest in drug use is increasing. Roberto Williams Garcia describes a communal curing ceremony among the Tepehua (6), who live in scattered communities in the mountains of Veracruz, Hidalgo and Pueblo, and belong linguistically and culturally to the Totonac of Veracruz, northernmost branch of the Mayan language family.

The curing ceremony is centered around a plant called santa rosa, "The Herb Which Makes One Speak," and Garcia identifies this plant botanically as Cannabis sativa. According to this investigator santa rosa is considered both as an herb and as a special intercessor with the Virgin. It is worshipped as an earth deity and is thought to be alive and comparable to a piece of the heart of God. It is also dangerous - were it not for prayers and rituals, it could affect people adversely. It could assume the form of a man's shadow (soul) and make him sick, put him in a rage, or even lead to his death.

Although the ceremony is conducted by a shaman, the central portion of the ritual involves the consumption of the herb by all the participants. The female participants dance in a circle and speak in a high voice. The atmosphere during this part of the ceremony is not at all solemn, but later on the atmosphere changes to one of fervent music, dancing, ringing of bells, impassioned oratory, and prayer. The shaman prays, and then dances with a

handkerchief, an act signifying that all children in the village suffering with grippe are cured. The ceremony lasts a good part of the night.

A North American ethnobotanist who has spent several years in Oaxaca provides another illustration of the acceptance of a comparatively new hallucinogenic plant in an area which has had extensive experience with the magic mushrooms. The experienced farmers in this area have discovered that the finest cannabis is derived from plants that have been "tortured" by an extreme environment and unusual pruning practices. When the plants are just beyond the seedling stage, they are pinched to remove the apical meri stem which terminates the shoot tip. This part of the plant is responsible for the production of auxins, plant hormones, and the absence of this site of synthesis causes side shoots to become active. This results in the production of a small bush, instead of the usual tall cane. This pinching continues every week, so that it never rises more than a few feet from the ground. The plant assumes an urn shape in the course of such pruning. Shoots which would normally fill the interior are removed, so that as resins are formed they volatilize within the confines of this urn-like shrub.

At maturity the "urn" is so coated with resins that the surface of the plant has a crystalline appearance. The normal flowering of the female plants is interfered with because of the frequent pinching, and the auxin changes sometimes lead also to a change in pigmentation. Cyanins, which give a red appearance to plants, may accumulate, giving the plant a peculiar color as well as form. The mode of harvesting as well as cultivation departs from the normal. As the blood-like color begins to appear the plants are "crucified" by inserting wooden splinters through the stem at right angles to one another just above the ground. The resultant material, which acts rather like hashish, is used exclusively in the area in which it grows for ritual purposes akin to those involving the use of indigenous hallucinogens.

Central America - Guatemala

The First National Conference for the Study and Evaluation of Drug Problems (June 1972) was inaugurated by the President against a background of increasing official concern (but little actual knowledge) of the drug problem as reflected in the recent upsurge of arrests. The conference received extensive press coverage for several days prior to its opening, throughout the conference, and has been followed by numerous drug related articles and editorials. One of the more significant press contributions to the conference was the report of a survey by one of the local newspapers which stated that six percent of the secondary students use, or have used drugs, and listed those places (by category) where those drugs are most easily obtained. The accuracy of the information can be called into question given the nature of the sampling and collection techniques used - still it is the only available information on drug use in the country.

South America

Chile

Two studies have been published within the past year concerning student marihuana use in Chile. There is no record of indigenous group use in that country, and national interest and concern apparently began about 1968. One study was conducted at a coeducational high school, with an equal number of boys and girls, and an age range of from 13 to 18. (8) The authors do not give any socioeconomic data other than the educational levels of the parents, of whom 63 percent had finished high school, and 44 percent had college degrees. The investigators used a 61 item questionnaire, divided into three categories. The first section consisted of essentially demographic information, although it also included questions on religion and church attendance. The second section contained questions on use of alcohol and tobacco, and the third section was devoted exclusively to marihuana - levels of use, effects, motivations for use, or desire to try and so on.

The level of use among these students is much lower than their counterparts in other parts of the Americas. Of 732 students who completed the questionnaire, only 51 or barely 7 percent had ever smoked and of these, 31 had smoked only one or two cigarettes. A little over 17 percent of the students, 118, stated that they would like to try marihuana. A comparatively high proportion of student smokers reported adverse reactions to the drug which the investigators feel may be due to lack of knowledge of the drug.

Argentina

Argentina has asked for help from the United States in setting up programs for educational, rehabilitation and assistance programs. They view this as a two-way process, with Argentine psychiatrists and social workers coming to the U.S. for short visits to observe methods used here, and U.S. experts going to Argentina for more extended periods of time to help in inauguration of prevention and education programs.

The Caribbean - Jamaica

The material in this section is an adaptation of the findings from an extensive study of ganja use in Jamaica carried out by the Research Institute for the Study of Man, in cooperation with the University of the West Indies from August 1970 to December of 1971, under the aegis of the Center for Studies of Narcotic and Drug Abuse of the National Institute of Mental Health. Ganja is a strong form of marihuana.

Research topics included a study of the anthropological, medical, psychological, and psychiatric effects and parameters of use and nonuse of cannabis. Basic background studies of cannabis use in seven ecologically different communities were conducted by teams of anthropological field workers from June 1970 through

December 10, 1971. In collaboration with the Faculty of Medicine of the University of the West Indies, and under the special sponsorship of Dr. Michael Beaubrun, Professor and Chairman of the Department of Psychiatry, thirty smokers and thirty controls were admitted to the hospital for a period of six days to undergo a series of intensive medical, psychological, and psychiatric examinations. The subjects ranged in age from 23 to 53 and were drawn from the working class strata of Jamaica: farmers, fishermen, artisans, and tradespeople. Smokers and controls were matched for age, socioeconomic status, and residence. Comprehensive life histories were recorded for each subject.

The results of the physiological, psychological, and psychiatric tests are reported in another section of this report. We shall be concerned here with the anthropological findings (a term to be considered in its widest applications since the researchers have attempted to examine many facets of the entire socio-cultural matrix of ganja use). This study has aroused widespread interest in the anthropological community (ethnologists are now exploring or have explored the possibilities of doing cannabis research in at least five other countries) as well as concerned governmental bodies, particularly those in the neighboring islands of the Caribbean. Penalties for ganja use have been reduced in Jamaica itself as a direct result of the study.

Young anthropological graduate students (from the United States and Jamaica) worked in the field under direct supervision of senior anthropologists (a departure from the usual anthropological practice of unsupervised field work). This has created an important pool of young workers who could be profitably used to carry on, in other cultures, the much needed basic groundwork for any truly valid cross cultural research in cannabis use.

Documentary evidence points to the fact that cannabis (as well as the multitude of uses to which it could be put) was introduced by East Indian contract laborers who were brought to Jamaica about 1845. The name used is "ganja," an East Indian term. There is use of chillum pipes as well as "spliffs" (cigarettes) for smoking; and, there is pragmatic as well as ritual use (ganja plays a role in folk medicine which is equally as important as the role it played and continues to play in Indian folk medicine).

The whole socio-cultural complex of beliefs about ganja use was probably diffused to the Negro population through contact with East Indian laborers on the sugar plantations. The lower class native Jamaican seems to have embraced the use of the drug because it served significant psychosocial as well as economic functions.

Today the principal users of ganja, usually called herbs (bad herb means cannabis of high potency) are still found to be among the lower classes, although, in common with most other countries of the world, more and more users are being drawn from the middle and upper classes. Users of cannabis in these classes speak of marihuana and probably the route of diffusion for these users was through the United States, England, and Canada.

Ganja is smoked, occasionally chewed, taken in "bush teas" for a wide range of ailments, as well as to build up strength, and cooked as a vegetable or added to soups, stews, and sweets. Smoking is usually confined to men, but children are introduced to ganja quite early through the medium of bush teas. This use may even start at birth, because some midwives in rural areas may recommend that an infusion of ganja be rubbed on the fontanell of the newborn infant to assure "wisdom," and also insist that the neonate be washed down with "ganja" tea to give him "strength" and prevent marasmus.

The use of ganja in the bush teas is almost universally accepted, and many persons who are loud in their denunciations of ganja smokers may regularly use the teas. Use of ganja in beverage form is never connected in any way with questions of social deportment--for example, it is never the tea drinkers who are accused of crimes or bizarre or psychotic behavior. It is never the ganja tea drinkers who are the object of periodic public crackdowns.

Ganja smoking is extremely widespread among lower class Jamaicans--Dr. Beaubrun estimates that about 40 to 50 percent of the adult males could be considered regular users. It should be remembered that there is an extremely small middle and upper class on the island. The use of ganja seems to be situation specific - it can be used to give extra energy and stave off fatigue, or it can be used to induce restful slumber - it can reduce or increase appetite and so on. By far the most compelling reason given for the use of ganja by smokers other than those in their adolescent years has to do with its capacity to give energy - "it makes you feel to work." This finding is particularly important in view of the preoccupation of investigators in the United States and other industrialized Western nations with the so-called amotivational syndrome. This aspect of ganja use was studied not only through interview data, but also through videotaping of actual work behavior in a farming community with and without the use of ganja, under normal conditions to see whether the perceived increases of energy levels actually takes place. The films prove that there is no actual increase in energy, and in fact, there may be a decrease in work output. This investigator prefers the hypothesis (which may be applicable in other parts of the world as well) that this use may serve as a subconscious strategy for maintaining the community status quo in the face of ecological and population pressure on limited resources.

In general, the cultural expectations and the subjective experiences of Jamaican working class smokers bear little, if any, relationship to the so-called mind-altering, mind-expanding experiences so often described by American users. On the contrary one of the values most frequently ascribed to ganja by working class is "keeping conscious" which is seen as cognitive advancement and support for rational rather than instinctive behavior.

The age of initial use of ganja seems to have been steadily moving downward in the last ten years so that now the age of introduction for some boys may be as early as ten, although the modal age still hovers around the early teens. Smoking for boys is seen as a rite du passage, is generally a group activity, and has in it some of the elements of the thrill of illegal and disapproved behavior. As the user becomes older however, smoking tends to become part of his everyday round of activities.

The Far East

Two drugs, opium and cannabis, have a centuries old documented history of use in the countries of the Far East (India, Pakistan, Burma, Laos, Thailand, Ceylon, Korea, Vietnam, Taiwan, the Philippines, for the purpose of this discussion). In some countries, even those dominated by Moslem thinking, there is use of alcohol, a growing use of synthetic drugs, the amphetamines and barbiturates.

The countries under discussion (most of them underdeveloped) comprise a population of well over 972,000,000 embracing a diversity of populations, cultures, histories of divergent patterns of drug use. There is not a completely adequate census of drug users in any of the countries mentioned; indeed, in several of them there is no adequate population census.

In many of the countries, although use of cannabis and opium is technically against the law, it has been tolerated to a greater or lesser degree depending, in great part, on the country's awareness and receptivity to plans for reduction in drug use emanating from more advanced Western countries. Of late, as use has spread from the traditional user, the lower class male, to adolescents of the middle and upper classes, the countries have begun to respond to internal pressure to develop some mechanisms to deal with the growing drug problem. In addition, there are indications, in several of the countries, that there has been a shift in choice of drugs (from opium to heroin) as well as a shift in the method of use.

In almost all of these countries there is a significant lack of trained personnel in education, training, and treatment, in addition to inadequate treatment facilities. In many of them the presenting socioeconomic problems are of such magnitude that, until recently, little time or effort could be spent on dealing with the drug problem per se. More funds, proportionately, have been spent on enforcement, but there is increasing evidence that this approach has not served to stem the tide of rising drug use.

In previous years we have commented on drug use patterns in India, Pakistan, Afghanistan, Nepal, Korea, Vietnam, Thailand, Cambodia, Singapore, Hong Kong, and Japan.

In this year's report we have chosen to highlight only two countries, India and the Philippines, since the short dispatches indicate very graphically the problems faced by many of the countries in this part of the world as they attempt to grapple with the problems of drug abuse problems, in most instances, whose dimensions and parameters are unknown, and where the most familiar problem-solving devices stem from the police and the law courts rather than from the medical profession, the behavioral scientist, and the social workers. It should also be borne in mind in many of these countries that there is not the tradition of self-help through voluntary charitable agencies which exists in Western industrialized nations. Most action will have to be taken with government agencies which are, for the most part, understaffed and underfinanced.

With the opening of the channels of scientific information and exchange between Mainland China and the United States, it is to be hoped that information will soon be forthcoming not only concerning the methods which the government has used to reduce the number of opium users, but also any information about the use/nonuse of cannabis in that country. Since China is one of the first countries in the world in which there is documented information on the use of cannabis for medical purposes, and we know that there has been extensive fostering by the government of interest and use of native medicinal herbs, it would be of interest to know whether cannabis continues to be employed, and in what ways, in either folk medicine or by the establishment.

India

A two-day seminar on Drug Abuse and Youth held in New Delhi in July 1972, was attended by some 75 delegates and 60 observers representing governmental and private agencies concerned with the health, education and welfare of children. All observers agreed that the problem of drug use is growing among Indian students, primarily those coming from upper class families, but no firm statistics are available.

The seminar made a series of recommendations which they planned to submit to the Government for early implementation. These recommendations include the following items:

1. Research studies be launched immediately to identify in the Indian context the dimensions and causes of drug abuse among young people (students and workers) in both urban and rural areas.

2. Establishment of an interdisciplinary committee of experts, administrators, law enforcement officials, and social workers to serve as an advisory committee to the Government for policy-making in the prevention of drug abuse and addiction.

3. Development of a concerted preventive program by the Government departments of health, education and social welfare with special emphasis on family responsibility of parents towards their children.

4. Legal action should be confined mainly to drug peddlers; young persons found to be using drugs should be treated in special psychiatric clinics.

5. Representatives of the mass media should be involved in a planned campaign to inform the public of the dangers of drug abuse.

The delegates to this convention, which was open to the general public, were generally much concerned about the growing incidence of drug use and abuse among Indian young people, but handicapped in trying to establish a firm

policy since there were no reliable statistics available on the nature and extent of the problem throughout the country.

In September the Delhi Medical Association, in cooperation with the Directorate of Health Services, Delhi Administration, and the Ministry of Health, held a one-day seminar on drug abuse. Mr. P. S. Ramachandru, the Drug Controller of India, asked for more effective control by the Government over the cultivation of cannabis.

Presumably in response to these two seminars the Central Government acted promptly to begin implementation. The Ministry of Health has appointed a special committee to consider measures to tighten up the regulations concerning the distribution and sale of narcotics and psychotropic drugs. Drug manufacturing firms have been directed to discontinue free distribution of certain types of tranquilizers and other drugs as physicians' samples. Publishers of medical journals have been urged to emphasize that chemists and drugstores may supply psychotropic drugs only on presentation of bona fide prescriptions from qualified doctors. State Government Drug Controllers have been instructed to keep a closer check on the activities of retail druggists.

The Philippines

Prior to World War II widespread drug dependence (7) was unknown in the Philippines, but in the last 35 years, particularly in the last ten, the abuse of drugs has become a serious national problem. A recent report by the Chief of the Narcotics Division estimates that at least 60,000 young people are engaged in drug experimentation. The main drug used is marihuana, and there are indications that some local dealers are growing their own supplies. Cannabis plantations have been found in the Manila area as well as in Caloocan City, Quezon City, Las Pinas, Rizal and Cavite. There are also some plantations on neighboring islands such as Negros, the Bicol Region, Mindanao and Central Luzon.

The National Mental Hospital and related treatment centers in other regions of the Philippines have numerous patients, from various social classes, admitted for dependence on a variety of drugs including heroin, morphine, cocaine, amphetamines, barbiturates and tranquilizers. One treatment center, located at Tagaytay City, and run by the National Bureau of Investigation, currently houses about 80 addicts (dependent on morphine and heroin) who come from Tondo, a slum area of Manila.

The Addiction Institute of the National Bureau of Investigation provides detoxification, psychiatric service, vocational guidance and follow-up domiciliary care for any addict who requests it. In addition, a new organization, The Narcotic Foundation of the Philippines, has been formed. This is a private organization primarily devoted to the raising of funds for the treatment and rehabilitation of young addicts as well as to launch various drug education and prevention programs.

At the end of March 1972, President Marcos of the Philippines signed into law the Dangerous Drugs Act of 1972, thereby providing the country with necessary new legislation to allow the country to deal with its growing drug abuse problem. The passage of the Bill and its signing brought to a close a process which had begun early in 1971 when new narcotic legislation was introduced into both houses of the legislature. In 1971 the House passed the Bill, but the Senate failed to bring it to a final vote. However, early in 1972 the first piece of legislation the Senate passed was the Dangerous Drugs Act. The Bill enjoyed wide support and its legislative course was remarkably free of the partisan politics that frequently affect major legislation in the Philippine Congress.

The legislation creates a national Dangerous Drugs Board to implement the provisions of the Act. This nine member Board will be composed of three experts appointed by the President and, as ex-officio members, the Secretaries of Justice, National Defense, Health, Education, Finance and Social Welfare or their representatives. Among other duties this Board is charged with the development of educational drug abuse programs for the general public, the provision of special training for police agencies, school authorities and personnel of rehabilitation centers, the conduct of research on dangerous drugs, preparing and coordinating the implementation of a national treatment and rehabilitation program.

In general the Act emphasizes harsh penalties for those who engage in illegal production or trafficking in dangerous drugs, and stresses rehabilitation for drug users. Within the first six weeks of the passage of the legislation, more than ten persons have been convicted on charges of illegal possession or use and selling of dangerous drugs with sentences ranging from six months to twelve years. This upsurge of harsh sentences, many of them given out to middle class persons, has created a flurry of public debate about how severely the law should be implemented against users. Several Senators who co-sponsored the Senate version of the Bill have already called for amendments to insure that drug users receive treatment rather than prison sentences.

The country is woefully short of resources both on the enforcement and rehabilitation, education ends of the continuum. According to press reports, President Marcos has been unable to find qualified persons to fill the three permanent positions on the Dangerous Drugs Board, and until he does, most of the educational and rehabilitative programs called for by the Act are unlikely to be started.

References

1. Bueno, D.U., M.D. The Problem of Drug Addiction in Mexico. In R.T. Harris, W.M. McIssac, and C.R. Schuster, Jr. (Eds.) Drug Dependence. Austin, Texas: University of Texas Press, 1970.

2. Blum, R. Society and Drugs. San Francisco: Jossay-Bass, 1969.

3. Buikhuisen, W. and Timmerman, H. The development of drug-taking among secondary school children in the Netherlands. Bulletin on Narcotics, 24:3-16, 1972.

4. Cannabis - A Report of the Commission of Inquiry into the Non-Medical Use of Drugs. Ottawa: Information Canada, 1972.

5. Drug Trafficking and Drug Abuse Report from the Senate Select Committee. Canaberra: Australian Government Publishing Service, 1971.

6. Emboden, W.A., Jr. Ritual Use of Cannabis Sativa L: A Historical Ethnographic Survey. In: P. Furst (ed.) Flesh of the Gods. New York: Praeger, 1972.

7. Goduco-Auglar, C. A note on drug abuse in the Philippines. Bulletin on Narcotics, 24(2), 43-44, 1972.

8. Gomberoff, M. A study of the conscious motivations and the effects of marihuana smoking on a group of adolescents in Chile. Bulletin on Narcotics, 24(3), 27-33, 1972.

9. Soueif, M.I. The social psychology of cannabis consumption: myth, mystery and fact. Bulletin on Narcotics, 24(2), 1-10, 1972.

10. Soueif, M.I. Hashish consumption in Egypt, with special reference to psychosocial aspects. Bulletin on Narcotics, 19(2), 1-12, 1967.

PRECLINICAL RESEARCH

This section summarizes a wide range of investigations, chemical, biochemical, pharmacological and behavioral. Studies reported this year have included evaluation of the effects of repeated as well as single administrations of cannabinoids and give us a better picture of what can be expected in long-term use in man. Tolerance to many of the effects of cannabinoids has been reported in long-term studies, but there is still disagreement regarding the mechanisms involved in the production of tolerance.

One of the most important findings this year has been to confirm in animal studies that synthetic or natural marihuana appears to have no serious deleterious effects on pregnancy, the fetus or the newborn. While such evidence cannot categorically rule out such effects in humans, it is nevertheless reassuring.

Although many of the cannabinoids isolated from marihuana have become available through synthesis, there is still considerable interest in the plant itself, the factors influencing its variations in potency and the biosynthesis of its active components.

Considerable research also continues in the analytical area towards development of new techniques, such as radioimmunoassay, for detection and quantification of cannabinoids.

Studies of cannabinoid metabolism have continued at an accelerated pace. It is now certain that cannabinoids are rapidly transformed in the body and there are now at least twenty-two known metabolites of marihuana that have been identified either in vivo or in vitro. However, there is not yet conclusive evidence about which metabolite or metabolites are responsible for the psychological effects of marihuana in man. Considerable effort has been made to develop large scale syntheses of these metabolites, especially of the 11-OH metabolite of delta-9-THC but progress has been slow. Metabolites are still being produced on a very limited scale, in milligram amounts. This scarcity of materials has so far prevented in depth pharmacology studies of these compounds. Nevertheless, it has been confirmed this year that the 11-hydroxy metabolite of delta-9-THC is a potent psychoactive agent and its effect at least equal to that of the parent compound.

The abuse potential of delta-9-THC is still under debate with one study reporting some "abstinence signs" in a small number of animals upon discontinuance of the drug. In the same study, some of the monkeys were able to initiate and maintain self-administration of THC while in another study this did not happen.

It has been confirmed this year that biogenic amines, as well as cholinergic compounds, are implicated in the mechanisms underlying the effects of marihuana and that marihuana has definite effects on the neuroendocrine system.

In the past two years, a wealth of data has been published regarding the effects of marihuana on behavior. Reversal of behavior, from sedation to aggressiveness and fighting has been confirmed in the rat after long-term (more than two weeks) administration of doses of delta-9-THC at behavioral dose levels. This tendency towards aggressiveness seems to be increased by food deprivation. Cannabis seems also to induce an inversion in social hierarchy but is partially dependent upon the testing situations and the contingencies operating in the environments. The same is true of studies of the effects on cannabinoids on avoidance performance and behaviors maintained by aversive control which may or may not be affected by marihuana.

CHEMISTRY

In the First and Second Annual Marihuana and Health Report to Congress, (125, 126) detailed descriptions of the plant Cannabis sativa, its chemical composition and analytical methods used for detecting and assaying Cannabis and cannabinoids were given. In this Report, only the more significant developments that have appeared in the past year will be discussed.

Drug Sources

Although many of the cannabinoids isolated from marihuana and related materials have become available through synthesis, considerable interest and research continues with the plant itself, Cannabis sativa. In what might be a model study for all states, a detailed survey of a sample county in Kansas has revealed the extent of Cannabis growing wild (45). Further, various methods of controlling the plant were compared, indicating a variety of useful techniques. Additional studies showed the influence of seasonal and environmental effects on cannabinoid content (110). They confirmed the earlier studies showing that most native Cannabis is genetically derived from hemp producing varieties, which apparently have not changed significantly in their lack of ability to produce much of the active cannabinoid delta-9-tetrahydrocannabinol (delta-9-THC). This concept of low THC-producing varieties in this country may have to be revised in light of findings recently reported by Mishioka's group in Japan (152). By a massive screening of Cannabis varieties, they were able to find a strain that does not produce delta-9-THC, stopping at the biogenetic precursor cannabidiol (CBD). Cross pollination experiments with other strains always gave offspring that produced higher amounts of THC indicating that high THC-producing strains, e.g., Mexican, are genetically dominant, whereas the hemp varieties are genetically recessive. This may mean that the introduction of Mexican, etc., varieties may allow the common hemp varieties to become more "active." It has been observed that the Mississippi grown crops have shown higher THC contents in each succeeding crop (192), which may partially be a result of improved cultivation methods.

Yagi, of the Mishioka group, also reported direct evidence for the elucidation of the biosynthesis of cannabinoids in Cannabis (152). This was accomplished by finding a strain that was able to absorb and assimilate radio labeled precursors. Previous studies were hampered by the low levels of incorporation. Thus, the pathway as proposed by Mechoulam (138) but until now unsubstantiated, was shown to proceed from malonic and mevalonic acids and geraniol to cannabegerolic acid (CBGA) to CBD-acid to delta-9-THC acid. Also, in an alternate pathway CBGA is converted to cannabichrominic acid. The acids make up the largest amount of cannabinoid content in fresh marihuana and hashish and are decarboxylated on aging and smoking to THC, CBD, etc.

Although long known to be present in Cannabis products, delta-9-tetrahydrocannabinolic acid (delta-9-THCA) has only recently been isolated and characterized (40). In some samples investigated delta-9-THCA was present in a 5:1 ratio to delta-9-THC.

Further confirmations of the presence and properties of side chain homologs in hashish has appeared (50, 189). The propyl and methyl analogs of THC, CBD and cannabinol (CBN) were reported to have considerably lower activity than the parent amyl derivatives (189). It was recommended to give the propyl series the class name cannabivarol instead of the previously suggested name cannabivarin to avoid confusion with alkaloids and glycosides. The methyl derivatives were named as cannabiorcols.

Certain alkaloids of this type are known to have psychotomimetic properties, although it seems doubtful that the trace amounts present here would account for any of the effects of Cannabis products. Their complete characterization is required to settle this question. The roots of Cannabis have been examined and shown to contain triterpenes and a cinnamamide derivatives, which had weak analgetic properties (177).

The question of delta-9-THC stability has been extensively studied. Its conversion to the more stable delta-8 isomer occurs readily in the presence of acids, but apparently does not during smoking (187). The temperature dependence and mechanism for these conversions under various conditions have been studied (166). On porous surfaces exposed to circulating air, delta-9-THC was readily oxidized to CBN. Solutions in ethanol were found to be the best means of stabilizing delta-9-THC for long periods of time and have been shown to be stable up to one year (166).

A recent study of the effects of the smoking process on cannabinoid content showed that the decomposition of THC was not only dependent on the degree of dryness, the air current and temperature, but on the presence of other cannabinoids, e.g., CBD (30). If alone, as in spiked cigarettes, delta-9-THC was found to be affected to a much greater degree Earlier studies by a number of investigators give somewhat conflicting results (187). As the results depend on the techniques used, considerable caution must be exercised in their comparison.

Most of the synthetic and naturally derived samples of delta-9-THC, supplied to investigators, contain small amounts of delta-8-THC and CBN. Earlier samples also contained the exocyclic isomer, delta-9,11-THC, but this was later eliminated as manufacturing technique improved. A microparticulate gel chromatography method is recommended as a convenient technique of obtaining small quantities of pure delta-9-THC in the laboratory (167).

Intensive efforts have continued towards improved and new synthetic methods for obtaining biologically significant cannabinoids. This important work is providing limited quantities of some of the less readily available natural cannabinoids and metabolites for research purposes. It is essential to understand the biological properties of each to gain a clear picture of the overall effects of Cannabis. For example, there have been reported the synthesis of delta-9,11-THC (161) and the active metabolites 11-hydroxy-delta-8-THC (151), and 11-hydroxy-delta-9-THC (193). Also new syntheses of radiolabeled THC's have appeared (66, 116).

Analytical Techniques

Considerable activity continues in the area of developing new and more refined technique for the detection and estimation of cannabinoids and their metabolites. Such methods are important for forensic and screening purposes and for determining biological levels and distribution of the cannabinoids. Gas chromatography continues to be the technique most widely employed. Its characteristic sensitivity and separating abilities have been steadily improved upon. By using a solid sample injection system the contents in as little as 1 mg. of dried plant material may be quantified (165). The use of more easily detected derivatives (175) and a survey of suitable conditions (86) have been reported.

One of the other techniques that continues to be investigated is thin layer chromatography using highly flourescent cannabinoid derivatives. Although very useful for the analysis of chemical mixtures, the method has still not been perfected for use with biological samples, e.g., urine or blood (54). Radioimmunoassays (RIA) continue to command intense interest as they would provide a highly sensitive and convenient method of detecting cannabinoids in biological media. Unfortunately, a number of problems continue to plague the development of a suitable method. Progress has been made on fluorescence quenching (71) and other immunological techniques (188) and a suitable universal method appears imminent.

The use of an automated process based on a new technique of mass fragmentometry has been reported (72). A simple method of detecting Cannabis smokers by breathing onto strips of a test paper impregnated with Fast Blue B dye has been suggested (133). It is sensitive up to two hours after smoking although some tobaccos interfere.

Structure-Activity Relationships

Since last year's Annual Report, little additional information has been reported on the rather unique structural features associated with cannabinoid-like activity. The rather limited number of structural variations possible to retain biological activity only serves to dramatize the characteristic action of this series of chemicals. Often a detailed study of chemical features associated with the biological activity within a group of compounds can shed some understanding into their mechanism of action. This has not been true so far in the case of the cannabinoids whose stereospecific nature is indicative of very specific receptor interactions in the central nervous system (CNS). As yet, these receptors or sites of action remain to be elucidated.

Of particular structural interest is the growing body of information about the activity of cannabinoid isomers and metabolites, which will be discussed in further detail later. A comparison between the activity of delta-8- and delta-9-THC isomers and metabolites by intravenous and intracerebral administration in mice has been reported (21). Reportedly, they found that there is no difference in potency in their biological assay between delta-8- and delta-9-THC and that their principle metabolites, the 11-hydroxylated THC's, are nearly fifteen times more active by the cerebral route and twice as potent

even by the intravenous route. This agrees with other data that suggests that the metabolites are primarily responsible for the major pharmacological effects of the THC's. The more highly oxygenated metabolites were considerably less active as were CBD and CBN (21). Considerably more research is required in this area. In particular, details of brain levels, better controls and studies in other species are needed.

A number of synthetic analogs of the cannabinoids have been prepared and tested (166). These analogs contain an additional heterocyclic atom of nitrogen or sulfur. The nitrogen analogs were designed to have some relationship to other classes of compounds known to have CNS activity, e.g., stimulants, depressants, psychotomimetics and narcotics. These analogs have exhibited various degrees of these activities and do resemble the cannabinoids in a number of ways. The sulfur analog was quite similar to delta-9-THC (154). Further work with these and other analogs is in progress.

PHARMACOLOGY

In the last four years, there has been intense activity in the field of marihuana research. Significant aspects of the preclinical pharmacology of marihuana have been reported in numerous articles, reviews, and symposia (2, 41, 76), as well as reviewed in the last two Marihuana and Health Reports (125, 126). Controversy exists concerning several aspects, but progress is being made towards a better understanding of marihuana and its pharmacological effects. In view of the wealth of literature on marihuana and the two recent reports, no attempt will be made to conduct a comprehensive review of the preclinical pharmacology of marihuana. Rather, the preclinical pharmacological profile of delta-9-THC, the commonly agreed upon active component of marihuana, will be generally summarized and pertinent aspects emphasized.

Preclinical Pharmacological Profile

The effects of delta-9-THC in animals are best described pharmacologically as unique and complex. A variety of factors influence the ultimate response. Dose, vehicle, time after administration, prior sequence of administration, species, sex and environmental surroundings, all affect the response ultimately attributed to delta-9-THC.

The pharmacological syndrome observed is paradoxical in nature. In general, central nervous system depression is mixed with CNS stimulation, depending upon the dose and time after administration. For example, in rodents low doses of delta-9-THC or marihuana extract produce depression of spontaneous locomotor activity mixed with periods of hyperactivity. With larger doses, the animals are catatonic but paradoxically hyperreactive to sound or tactile stimuli (76). Analogous effects have been observed in dogs (95) and primates (1). Moreover, delta-9-THC interacts contradictorily with stimulant and depressant drugs. Reportedly, delta-9-THC potentiates the depressant effects of barbiturates and enhances the stimulation of locomotor activity produced by amphetamine (63).

Further complexity is introduced by the phenomenon of tolerance. Tolerance develops to at least certain behavioral effects of delta-9-THC in rats, pigeons, dogs, and monkeys; a comprehensive review of this phenomenon (137) was summarized in the 1972 Marihuana and Health Report (126). Recently, Pirch et al. have expanded these observations to studies of the effect of delta-9-THC and marihuana extract distillate (MED) on the rat electrocorticogram. Acutely, there was an overall decrease in integrated voltage, a decrease in the amplitude of low voltage activity, and the appearance of high voltage "spindle-like" activity after MED and delta-9-THC. Notably, when MED was administered chronically, tolerance appeared to develop to some, but significantly, not all of delta-9-THC's effects on the rat electrocorticogram (160). These, and many other studies, exemplify the complexity of the phenomenon of tolerance development to delta-9-THC or marihuana extract.

Recently, investigators have pursued the question of whether cross tolerance develops between delta-9 and ethyl alcohol in rats. Newman et al., proceeding from earlier reports of an interaction between chronic marihuana and ethanol's acute effects (137, 92), studied both drugs chronically in the rat (150). Reportedly, rats tolerant to delta-9-THC were less susceptible to the acute effects of ethanol in a one-way avoidance paradigm. Moreover, rats tolerant to ethanol were correspondingly less affected by delta-9. These results are intriguing both from a sociological and mechanistic viewpoint. A more definitive statement on this phenomenon, as well as its potential significance, will require further study.

In addition, this year, in contrast to earlier assumptions, self-administration of delta-9-THC was reported in the rhesus monkey (33, 93). After 36 days of chronic administration of delta-9-THC, two of six monkeys initiated and maintained self-administration of THC. Moreover, all six rhesus monkeys chronically treated reportedly demonstrated "abstinence signs" upon discontinuance of the drug. These signs consisted of hyperirritability, increased aggressiveness, muscle tremors and twitches, and yawning. Interpretation of this data is hazardous at best in view of the relative small number of animals which self-administered delta-9-THC, the severity of the treatment and the resemblance of the "abstinence signs" to chronic effects of delta-9-THC alone. Moreover, others have had difficulty inducing monkeys to self-administer delta-9-THC (77). Nevertheless, this observation is highly provocative and will undoubtedly stimulate further research along similar lines.

An early report of a specific antagonist to marihuana has been seriously questioned. A Russian account reported that phenitrone, [3-(hexahydro-1H-azepin-1-yl)-3'-nitropropiophenone HCl], appeared to block behavioral effects in dogs exposed to hashish smoke. However, subsequently, at least three groups have been unable to reproduce this effect in dogs, rats, or monkeys using more refined preparations of marihuana (119, 181). However, a somewhat related report of the blockade of the depressant effect of delta-9-THC in mice by cannabinol (194), although preliminary, has spurred interest in the possibility of finding antagonists to delta-9-THC.

Cardiovascular Effects

In contrast to the dose-related tachycardia observed in humans after administration of marihuana or the cannabinoids, bradycardia is generally observed in animals. In anesthetized dogs and rats, delta-9-THC produced bradycardia and long lasting hypotensive effects (39, 141). Spinal section of C_2-C_4 plus bilateral vagotomy reportedly prevents these effects (14). In contrast, however, atropine, ganglionic blocking agents, nor beta-blockers individually reportedly appear to be able to completely block these effects (36, 107). These and related data, reviewed in the last two Marihuana and Health Reports (125, 126), have prompted a number of investigators to postulate that the effect of delta-9-THC on the cardiovascular system is at least in part mediated centrally and that the characteristic effects of delta-9 are probably a result of diminished sympathetic outflow from the brain.

In the unanesthetized animal, however, although bradycardia is still observed, no significant hypotension is apparent (36, 109). Thus, it appears that at least the hypotensive component of delta-9-THC effect in the anesthetized animal is most probably a result of interaction between the anesthetic agent used and delta-9-THC.

Recently, Cavero et al. have performed a detailed analysis of the relationship between the respiratory and cardiovascular effects of delta-9-trans-tetrahydrocannabinol in the anesthetized dog (15). Using a relatively high dose (5 mg/kg), they showed that delta-9 induced transient hyperpnea and hypoxia in spontaneously breathing dogs, but not in artificially ventilated animals. Moreover, a marked and reproducible hypotensive effect occurred in the artificially ventilated animals not in the spontaneous breathers. In the latter, a diminished, more variable effect on blood pressure was evident. Thus, there appeared to be a relationship between the hypotensive effects of delta-9-THC and the maintenance of blood gas parameters within physiological values. The bradycardia produced by delta-9-THC, however, was similar on both groups of animals and therefore did not appear to be affected by these changes in ventilation. These results may explain some of the variability in results previously reported regarding delta-9-THC's effect on blood pressure.

Neurochemical Effects

In an attempt to delineate the mechanism of action of marihuana in the brain, a number of investigations have centered around the effect of marihuana extract or of the tetrahydrocannabinols on the brain biogenic amines. Initially, these concentrated on effects on whole brain levels of serotonin or norepinephrine. Now studies have been expanded to include analysis of turnover rates, localized sites in the brain, uptake and release mechanisms, amino acid uptake, and more recently to effects on other postulated neurotransmitters in the brain. A good deal of this work has been recently summarized in the 1971 Proceedings of the New York Academy of Sciences (186) and in last year's Marihuana and Health Report (126).

The voluminous literature on the effects of marihuana extract or the tetrahydrocannabinols on brain serotonin is quite contradictory. In 1964, Bose (2) reported a fourfold increase in whole rat brain serotonin after a single injection of marihuana extract. In 1965, Garattini (61) could find no alteration in serotonin levels in rat brain following either acute or chronic administration of cannabis extract.

Subsequent studies with pure delta-9-THC are still equivocal. Holtzman et al. (88), expanding these earlier observations, found that doses from 10-50 mg/kg i.p. of delta-9-THC produced a small, but significant, elevation of whole brain 5-HT levels in the mouse. These same dose levels produced a slight decrease in NE levels. Moreover, these changes in biogenic amine levels appeared to parallel the behavioral effects of delta-9-THC.

Later, two groups of investigators (194, 180), reproduced similar effects with respect to 5-HT, yet there was disagreement about the localization of the effect in the brain. Ho et al. (84) recently reported analogous results in mice after intravenous administration of 5-10 mg/kg of delta-9-THC. However, this group found that in the monkey IV doses of 2 mg/kg and higher produced decreases of both 5-HT and NE. In addition, delta-8-THC exerted a greater effect on both biogenic amines despite the fact that delta-9 appeared more potent behaviorally. A somewhat related contradiction was reported by Welch et al. In their studies, cannabinol (CBN) exerted an effect similar to delta-9 on telencephalic serotonin in the mouse (194).

Other groups (60, 113) have recently reported that there appears to be a dissociation between the behavioral effects of delta-9-THC in the rat and alterations in brain serotonin. An analogous result was found in mice (95). Although the behavioral effects of delta-9-THC were evident at the doses studied, no statistically significant change was observed in 5-HT levels.

The effects of cannabinoids on catecholamines have also received their share of attention. At least three groups (174, 194, 113) have been unable to confirm the previously reported decrease in norepinephrine levels. Studies are proceeding on more complex measures of NE effects in the brain. As previously summarized (186), the schedule of administration of ^{3}H-NE and THC seems to affect the results on norepinephrine. Increased retention of ^{3}H-NE appears evident if THC is administered first (186); conversely if the tritiated NE is equilibrated prior to THC, there seems to be an increase in NE turnover at least initially (186, 122). Moreover, other investigators have found increased catecholamine levels in specific brain areas using fluorescent histochemistry (26, 143, 59). These findings in specific areas of brain may ultimately explain some of the differences observed in studies on alterations of whole brain biogenic amines. A dopaminergic mechanism has also been recently implicated in the behavioral effects of delta-9-THC (57). Following acute and chronic (8 days) i.p. injections of 5 and 10 mg/kg delta-9-THC in rats, endogenous levels of dopamine were reduced in the brain stem, but not in the forebrain. Homovanillic acid levels were elevated by acute delta-9-THC.

In addition to studies on NE and 5-HT, there has been some investigation of effects on other postulated neurotransmitters. Domino et al. (41) recently

reviewed the effects of delta-9-THC on acetylcholine (ACh). In two strains of mice, increasing doses of delta-9-THC reportedly produced a statistically significant increase in whole brain acetylcholine; correspondingly, at least two dose levels (10 and 32 mg/kg) delta-9 antagonized hemicholinium induced reduction of ACh. Expansion of these results to an analysis of effects on ACh release from the cat cortex revealed that, although increased variability was apparent with small doses, larger doses of delta-9, as expected, seemed to cause a progressive decrease in ACh release. These results, it was amply pointed out, are complicated by the fact that most central nervous system depressants increase acetylcholine levels at doses producing sedation and comatose state.

A preliminary report (113) indicated that changes in gamma-aminobutyric acid (GABA) levels occur in the mouse brain after delta-9-THC. Leonard, in a series of comprehensive articles on the effects of psychotropic substances in the brain amines (112, 113, 114), reported that a large dose (100 mg/kg i.p.) of delta-9-THC, producing pronounced behavioral effects in rats, caused a slight decrease in brain and blood tyrosine and brain GABA levels, although the levels and turnover of other important amines appeared unchanged (113).

In the last two years with increased information about the effects of delta-9-THC on biogenic amines in the brain, it has become evident that this is a very complicated area of investigation. In addition to the complex pharmacological profile of delta-9-THC and the marihuana extract, the central nervous system is a dynamic system with intricate mazes of biochemical events. Levels of biogenic amines are maintained by multifactorial events including uptake of precursor amino acids, activity of synthetic and degradative enzymes, uptake and release mechanisms, as well as the interaction of various functional neuronal systems in the brain. Evidence is increasingly accumulating to show that delta-9-THC and marihuana extract influence both steps directly involved with maintenance of amine levels as well as related steps (91, 134). Interpretation of the data now tends to emphasize changes in the overall balance of levels of biogenic amines (84) rather than discrete changes in the whole brain levels.

Neurophysiological Effects

Additional studies of the neurophysiological and neuropharmacological effects of cannabinoids in various species, rats (160), cats (176), rabbits (58), and baboons (100) have been reported in the past year.

Evaluation of the effects reported in the different studies is, as usual, different since various dose levels, routes and experimental conditions were used. When one considers, however, the results obtained by the IV route, a typical pattern of marihuana effects on the EEG seems to emerge. As shown by Segal (176), it appears to consist of a triphasic EEG response characterized by an early stimulation and increase in arousal, then depression shown as cortical synchronization simultaneous with or followed by high voltage spiking activity. Cortically, the effect seems to be more intense in the frontal than in the posterior areas. Subcortically, the cannabinoids produce

definite changes in the "old brain" areas. In the hippocampus, changes in rhythm (117, 19), epileptiform spikes, slow waves (127, 117), and fast, high amplitude spindles (85, 19) have been reported. Spindles were also seen in the amygdala and hypothalamus (85). The effect of cannabinoids on the septal region is mixed, with sometimes stimulation (fast spindling activity) and at other times depression (slowing with sharp waves) (78, 19). The marked effect of the cannabinoids on these areas is not surprising in view of the autoradiography findings showing high concentrations of delta-9-THC or its metabolites in these subcortical areas (83).

In rodents, delta-8-THC produces the same effects as delta-9-THC (145), but, in the cat, delta-8-THC produced EEG depression rather than the activation seen with delta-9-THC (176, 191). Repeated daily administration showed some tolerance developing to the EEG changes in voltage but not to the spike-like activity (117, 160). Although this spike-like activity has been a consistent finding in most studies (117, 191, 176, 42, 127), there has been no report of seizure activity after acute administration of cannabinoids, even at high dose levels. It has even been shown (100) that small doses of 5-160 micrograms per kilogram of delta-9-THC, which produce changes in spectral power density distribution of resting EEG patterns in the baboon, can block photomyoclonic evoked seizures, corresponding to the findings of Sofia who has reported an anticonvulsant effect of cannabinoids (179).

The neuroendocrine effects of marihuana on the hypothalamo-hypophyseal-adrenal axis have been reemphasized. Oral or i.p. administration of hashish to rats produces an increase in plasma corticosteral levels in plasma corticosterone and depletion of adrenal ascorbic acid and cholesterol content (37). This corticosterone elevation by delta-9-THC had previously been shown to be centrally mediated (108). Others investigated the effects of orchidectomy and testosterone pretreatment on responses to marihuana (22). These experiments demonstrated that responses to marihuana may be altered by changes in hormonal balance.

In Vitro Effects

A. Liver

Delta-9-THC strongly affects rat liver mitochondria *in vitro*.

> "At concentrations of 15-60 nanamoles/mg of mitochondrial protein, THC uncoupled state IV respiration and decreased respiratory control and ADP/O ratios. Energy-linked changes in fluorescence of 8-anilino-1-naphthalene sulfonate were prevented or reversed by THC. THC also produced large amplitude swelling of mitochondria and release of matrix enzymes. These effects were greatly potentiated by Mg^{2+}. Likewise, flocculation of mixed phospholipid micelles by Mg^{2+} was potentiated greatly by low concentrations of THC. Studies with micelles prepared from purified phospholipids suggest that THC may specifically destabilize the cardiolipin in mixed micelles."

It also increases ATPase activity (17). In vivo, delta-9-THC increases the activity of two liver enzymes, tyrosine-alpha-ketoglutarate transaminase (FKT) and tryptophan-pyrrolase (TPO).

B. Lung

Addition of marihuana to cigarettes has been shown to produce a smoke which evokes morphological and cytochemical alterations in epithelioid cells of lung explants such as atypism, mitosis and DNA synthesis to a significantly greater degree than does smoke from cigarettes without marihuana (115). In isolated perfused lungs, delta-9-THC decreased perfusion flow rate, indicating pulmonary vascular constriction and increased tidal volume, probably by primary action on the alveoli (182).

C. Red Blood Cells

Delta-9-THC protects red blood cells against hypotonic hemolysis. This protection increases with increasing THC concentration. Lowering of either pH or temperature enhances the stabilizing effect. Addition of albumin to the hypotonic solution decreases stabilization. This protective effect of THC is probably due to its highly lipophilic character and low water solubility, which probably help it to bind erythrocytes membranes (16).

METABOLISM

Intensive efforts continue in the studies of cannabinoid metabolism. In addition to attempting to learn about the absorption, distribution and fate of the drugs themselves, far more information about the pharmacologic properties of their metabolites is required to understand clearly the overall effects of Cannabis and its derived products. Various aspects of Cannabis metabolism have been reviewed since last year's report (148, 148a, 190). Absorption, distribution, metabolism and excretion will be discussed separately.

A. Absorption. Little new information concerning the relative efficiency of various routes of administration has appeared. It is commonly accepted now that administration by inhalation (smoking) and intravenous injection are the most effective routes, with oral and intraperitoneal not as good. Studies using intracerebral injections (21) indicate more accurately the central effects of the parent drug as they have also shown that little if any metabolism takes place in vitro in the brain tissue (21). One must regard these results with caution, however, as the drug passes freely out of the brain into the circulating system where it can be metabolized and the metabolite can enter the brain.

Other water-soluble derivatives suitable for oral and parenteral administration have been reported (196). The most promising of these is the 1-(4-morpholino)-butyrate ester of delta-9-THC (SP-111A). It apparently hydrolyzes rapidly and gives effects nearly identical to the parent THC given in the usual emulsified form.

B. Distribution. Of continuing concern is the effects of Cannabis use during pregnancy. A number of studies on the distribution of THC and its metabolites in mice and pregnant mice have been reported (56, 75, 96, 170) By using whole-body autoradiography and measurement of radiolabeled drugs in isolated tissues, it has been unequivocally shown that THC penetrates the placental barrier and accumulates in the fetus and the cotyledons (153). The actual levels in the fetus are low, as they are also in the maternal brain and muscle, in comparison to the high levels in maternal fat, liver, spleen, lungs, adrenal and mammary glands, placenta and corpus luteum. At high doses, the fetal levels become high enough, however, to cause embryonic and fetal deaths (75). No differences were found between the distribution of delta-8- and delta-9-THC (170). The levels of THC in the brain following IV injection never attain a maximum, whereas the 11-hydroxy metabolites show a maximum at about 15 minutes (67, 170). Their half-lives in the brain, from a single dose, are 36 to 40 hours, respectively. The blood levels of THC and metabolites show a biphasic pattern of decline, with a second phase half-life of about 20 to 25 hours (170).

In the rat, repeated subcutaneous injections of delta-9-THC showed accumulations of THC and 11-hydroxy and 8,11-dihydroxy metabolites in (in decreasing order of levels): fat, liver, lung and brain (105). After a single injection the concentrations in body fats were ten times higher than any other tissue and persisted up to two weeks.

C. Metabolism. There are now at least twenty-two known metabolites of marihuana constituents. Of these there are eight each for delta-8-and delta-9-THC and three each for CBD and CBN. Many of these metabolites have been isolated or identified from human or animal administration, but a number have only been found to date from in vitro microsomal preparations. There is some variation in the pattern of metabolism in various species and this is an important factor to be considered when comparing the biological effects of the cannabinoids in different species. For example, from male dog liver, delta-8-THC was found to give rise to side-chain hydroxylated metabolites (132). In the rabbit, delta-9-THC was found to give in the urine 11-carboxylic acid metabolites with side-chain hydroxylation (5) In rats, from urine and feces, some glucuronide of delta-9-THC was found along with CBN, and 8,11-hydroxy-delta-9-THC was found in the urine as well (140). An unidentified diacetate metabolite was found in the bile. These studies, as are others, were conducted using a gas chromatography-mass spectrometry technique that can detect minute amounts of metabolites present in biological media but does not always permit their isolation and complete characterization.

In a recent study of the metabolism and excretion of delta-9-THC in the rat, experiments in which the bile duct was cannulated showed that as much as 60 percent of the IV dose was excreted via the bile, less than 10 percent in the urine and only 3 percent in feces (38) Oral administration gave over 40 percent of the excreted drug and very little metabolite in the feces, strongly indicating that at least one-third of the oral dose was not absorbed. This further confirms the role of enterohepatic circulation, as demonstrated earlier (101).

Of particular concern is the selection of a suitable animal species to serve as a model for man. From a metabolic standpoint, it would appear to date that this is best satisfied with the rhesus monkey. A comparison was made between the rhesus and squirrel monkey, but the latter was found to exhibit quite a different pattern of metabolism and excretion than the rhesus, which was quite similar to man (195). A study on the brain levels of THC and metabolites in the brains of squirrel monkeys has been reported, however (83). At thirty minutes after IV administration, about 4 percent of the dose was located in the brain, of which 84 percent was THC and 8 percent the 11-hydroxy metabolite. These levels went to 70 and 15 percent, respectively, at four hours.

Many of the findings about marihuana metabolism in animals are slowly being confirmed by studies in humans. This is important since studies in man are considerably more difficult and expensive to carry out.

Further support has been reported for the earlier hypothesis that the 11-hydroxy metabolite is the active form of the THC's (67, 111, 111a). A study of the blood levels following administration of delta-9-THC to twelve long-term marihuana smokers by IV, oral and inhalation routes showed that over 90 percent of the oral dose was absorbed and its metabolites gave a peak blood level at three hours (111a). The peak of metabolites by inhalation was over a range of 10 to 140 minutes, with an average of 70 minutes, demonstrating the extent of individual variation. These levels of metabolites correlated quite closely to the psychologic effects. In a study of the principal metabolite itself, 11-hydroxy-delta-9-THC gave psychological and pharmacological effects that were similar to THC, and lasted for several hours (111). The disposition and metabolism of the metabolite mimicked that of delta-9-THC as well. These studies were carried out with only three normal male volunteers and may require further confirmation before the question of the active species of drug is completely resolved. From a repeated dose study in man, it was reported that there was no significant accumulation of THC or metabolites appearing in the urine (87).

A study of the ability of the human intestine to metabolize delta-9-THC shows that this is another important site, in addition to liver and lungs, for metabolism (73). Because of its secretion in bile and with portal reabsorption, this site of metabolism must be considered significant regardless of the route of administration.

It seems from the metabolism studies to date that delta-8- and delta-9-THC and their 11-hydroxy metabolites are all active to varying degrees and account collectively for the overall effects observed after smoking or on administration of delta-9-THC.

TOXICITY

Comprehensive reviews of the toxicology of marihuana have been published recently (3, 52, 53, 147, 148, 148a).

Acute Toxicity

In rodents, it has again been confirmed that the therapeutic ratio of lethal dose to pharmacologically effective dose of delta-8- or delta-9-THC is very large (35). That study also showed that the choice of compounds used to suspend these insoluble substances is important as definite differences in pharmacological and even lethal effects were found when various suspending agents were used. A systematic study of the various solvents or suspending agents which can be used to administer cannabinoids by various routes, especially in the higher concentrations necessary for toxicity studies, has been published this year (169).

Two interesting Russian articles reported in detail the functional and morphological changes noted in experimental acute poisoning of fourteen healthy adult and young dogs given high lethal doses (1.5 - 4.0 grams/kg of body weight) of resin prepared from Yujnochuisk Cannabis (44). Stimulation alone or alternating with depression happened within thirty minutes and vocalization was followed by depression within two hours after administration. Impaired motor coordination, tremors, muscular rigidity, catalepsy and hyperkinesia were noted. Reportedly, acute Cannabis resin poisoning, whatever the dosage, affected the central nervous system and led to severe impairment of the animals' behavior and to the development of neurological symptoms. These symptoms were most intense in the early days, after which their severity decreased. Morphological changes in the brain were distinguished by disorders of the vascular circulation, which were a main constituent of the histopathological process. Degenerative changes such as hydropic degeneration and caryocytolysis, which could lead to the death of the cells, were seen in the cerebral cortex, medulla oblongata and cerebellum. The overall evaluation of histological experiments on acute Cannabis resin poisoning is that the pathological process is of the nature of toxic encephalopathy. Analysis of EKGs showed considerable and varied cardiovascular disturbance. Electrocardiographic and haemodynamic shifts which were observed during the first one to two hours - tachycardia, bradycardia, pronounced sinus arrhythmia, symptoms of coronary insufficiencies and reduced arterial pressure - were reportedly the results of damage to the vegetative centers and not to a direct toxic effect on the myocardium. Pathological changes were observed in the liver, kidneys and adrenal glands.

Clinical chemistry showed a decrease in red blood cells and an increase in leucocytes. Blood sugar, cholinesterase activity, and blood plasma protein levels rose and fell at different times.

Although the authors mention that these effects are similar to those of Indian Cannabis and their results in basic agreement with the findings of Chopra (18)

and Loewe (118), it is difficult to compare these findings with those of our American marihuana, as no analytical determination of the potency of the resin was made. Furthermore, the vehicle in which the resin was given is not mentioned and there do not seem to be any controls included in the experimental design

Another paper reported the first stage of a study on mice of the effects of chronic exposure to the smoke of marihuana or its resin-free residue (34). There were no significant differences in death rates of mice exposed to smoke from marihuana or residue and the LD_{50} was around two grams. Deaths were attributed to carbon monoxide poisoning.

Since delta-9-THC, like amphetamine, possesses some stimulating properties, the influence of conditions of housing on the toxicity of delta-9-THC was studied under different conditions. It was found that the lethal activity of a single intraperitoneal injection of delta-9-THC was significantly enhanced in isolated mice. Conversely, the toxicity of d-amphetamine was greater in aggregated mice while the mortality rate of chlorpromazine and phenobarbital was unaffected by housing conditions (179).

Chronic Toxicity

In view of the behavioral reversal from sedation to hyperactivity and aggressiveness found in our previous toxicity studies after chronic administration of even the lowest dose of delta-9-THC, i.e., 50 mg/kg, the National Institute of Mental Health decided to start a new and longer (six-month) chronic toxicity study of delta-9-THC in rats, orally, at lower dosage levels of 2, 10 or 50 mg/kg (28). After one month of chronic administration, the results were as follows:

Approximately 60 percent of animals on 10 mg/kg and 100 percent on 50 mg/kg displayed CNS depression in the first week of treatment. A dose-related decrease in respiration rate occurred. With the onset of tolerance in the second week, hyperactivity and passivity became prevalent and CNS depression was reduced. Irritability and fighting occurred at higher doses in the third week and the intensity of aggression was associated with the emergence of a dominant animal in each cage. Territorial aggression was manifested predominantly in male rats and was more apparent at 10 mg/kg than 50 mg/kg, probably due to the continuing tranquilizing effect of the higher dose. A poikilothermic effect was observed in response to higher ambient room temperatures. Anorexia and diminished water consumption in conjunction with a decline in growth rate occurred in the second and third weeks but were reversed in the fourth week at the highest dose. At necropsy, no drug related gross pathology was observed. Histopathology, hemotology and urinanalysis parameters were essentially normal. At high doses of delta-9-THC, adrenal weights were elevated in both sexes and the pancreas in the male. Apparent decreases in prostate and uterine weights were discerned with the possibility of a similar change in female pituitary weights as well. Neurochemical changes were somewhat variable and did not reveal any serious biochemical lesions in brain. It has been demonstrated for the first time that oral doses

of delta-9-THC (10 mg/kg) equivalent to those present in hashish evoke profound effects on the CNS manifested by fighting, starting within fourteen days after chronic administration.

After chronic I.V. treatment of monkeys with high doses of THC, O_2 uptake was measured in slices of cerebral cortex, midbrain, medulla, cerebellum and lungs in the absence and presence of succinate by conventional Warburg manometry. Endogenous respiration increased 16-30 percent in the brain cortex at doses above 4 mg/kg but not at higher doses. No change occurred in medulla. An apparent decline in endogenous lung respiration was not significant. Exogenous succinate consistently stimulated oxygen uptake, more so for tissues with low endogenous respiration, indicating no impairment of oxidative capacity This alteration in oxygen was only related to chronic intoxication with high doses of THC. This study also confirmed an earlier report that chronic parenteral administration of delta-9-THC, either by the intravenous or the subcutaneous route, produce edema, ulceration and fibrosis at the injection site, due to the caustic properties of cannabinoids (3, 184).

Very recently, toxic effects of marihuana tar in the mouse have been found. Confiscated marihuana was rolled into cigarettes and artificially puffed in a smoking machine. The smoke was collected and condensed, producing tar which was used for painting mice skin. A positive control group receiving benzo-(a)pyrene, a known carcinogen, was included in the experimental design. Marihuana tar, like benzo-(a)pyrene or cigarette smoke condensate in equal concentrations showed complete metaplasia of all sebaceous glands in mouse skin. The authors conclude that "since metaplasia of all sebaceous glands in the target area correlates well with carcinogenicity, it may be an indication that Cannabis tar will prove to be carcinogenic" (29). These findings confirm an earlier report by Magus (121) and indicate that smoking crude marihuana produces tar which, like that of tobacco and other plant materials, can be demonstrated to be carcinogenic by this type of technique. On the other hand, a comparative evaluation of the carcinogenic potential of the major cannabinoids of marihuana in another test system (transformation of cultures of rat embryo cells by combined action of murine leukemia virus and cannabinoids) showed that these compounds have a weak oncogenic activity compared to that of methycholanthrene (164).

In view of these conflicting reports, a long-term study of the potential oncogenic effects of cannabinoids seems in order.

Effects on Pregnancy, on the Fetus and the Newborn

One of the important questions regarding marihuana use in the population, which was clarified in the past year, concerns the effects of repeated dosage of cannabinoids during pregnancy and after birth in the mother, the fetus and the newborn.

As mentioned previously (125, 126), experiments in animals had produced conflicting results, with some authors reporting reduced fertility (142), stunting, fetal resorptions or malformations after administration of marihuana extracts

by various routes (64, 65, 75, 155, 156). Others (153), however, using delta-9-THC or extracts at dose levels ranging from 0.01 to 200 mg/kg for delta-9-THC, 20-40 mg/kg for delta-8-THC and 200-300 mg/kg of a marihuana extract containing 17.1 percent delta-9-THC, in a large number of experiments failed to find any abnormalities in offspring. In these studies, cannabinoids were injected at different times of gestation, using various solvents (olive oil suspensions, rat or rabbit serum or plasma plus propylene glycol) and two different species (rats and hamsters) in attempts to duplicate the experimental conditions used in the previously reported studies. The only adverse effect was that at high dose levels of 100 mg/kg and above, postnatal mortality was high in all groups as compared to controls. A cross-fostering experiment demonstrated that agalactia, i.e., lack of milk production in the mother, was primarily responsible for the death of pups, since placing some treated offspring with a control lactating female lowered the mortality rate, while the mortality rate of the control offspring placed with the delta-9-THC treated females was increased. Some of the offspring that survived were bred and the data indicate that there was no fertility impairment in the F_1 and F_2 generations and no development of abnormalities in the offsprings. Unfortunately, the subcutaneous route of administration was used in this study. It has since been shown to be a rather poor route of administration for repeated administration of cannabinoids since repeated injections produced erythema, edema and granulomas at the injection site due to the caustic properties of the cannabinoids (3). There is also some doubt regarding complete absorption of cannabinoids by this route, although the authors had previously shown that delta-9-THC affected the rats' spontaneous activity and depressed bar pressing within 10 minutes after s.c. administration at the same dose levels (144).

In view of these conflicting reports a year ago, the National Institute of Mental Health initiated a comprehensive study of the effects of delta-9-THC and a crude marihuana extract in two species to determine their teratogenic potential as well as the effects of these compounds on reproductive functions and on the newborn. These studies were made in rats and rabbits, at dose levels which do not markedly affect the body weight gain of normal animals. This is important and was not carefully controlled in other studies which have instead used doses as high as 1/2 of the LD_{50}. In such cases, effects on reproduction and fetal development become confused with general toxicity. The NIMH studies were conducted according to the Food and Drug Administration Guidelines and divided into three phases: prenatal (Phase I), potential for teratogenicity (Phase II) and postnatal effects (Phase III). Phases I and III were conducted in rats only, Phase II in rats and rabbits. Rats were dosed with 0.5 mg., 1.5 mg. and 5.0 mg. of delta-9-THC/kg. of body weight given either as the pure compound or as an extract containing 16 percent of delta-9-THC. Dosing was initiated sixty days prior to mating for males and fourteen days prior to mating for females in the Phase I studies, and on day 15 of gestation in the Phase III studies. Drug administration to the parent animals was continued until sacrifice. The results were as follows:

A slight depression in body weight gain was observed among rats given 5 mg/kg. Behavioral reactions observed among rats from all treatment groups included inactivity, irritability, pallor and pupillary constriction. The severity and direction, but not the incidence, of these reactions were dose related.

An apparent tolerance was manifested by a decrease in the severity and duration but not complete absence of these reactions. There were no treatment related mortalities. Mating and fertility indices were similar for the control and all treatment groups. At the interim sacrifice, on the fourteenth day of pregnancy, the numbers of corpora lutea, implantation sites, and live fetuses were similar for all groups. The average numbers of pups delivered and viable at birth did not differ among treatment and control groups. There were no statistically significant differences in the number of live pups on lactation days 1, 4, 12 or 21.

To determine the teratogenic potential of delta-9-THC and of marihuana extract, pregnant rabbits were dosed orally from days 6 through 18 of gestation with 0.5, 1.5, 5.0 or 15 mg. delta-9-THC/kg body weight from either source. Pregnant rats were dosed orally from days 6 through 15 of gestation with 5, 15 or 50 mg/kg delta-9-THC/kg body weight. A positive control group treated with 37.5 mg/kg of Thalidomide was included in the experimental design. Sedation and depression of body weight gains was seen in females at the high dose level. The number of live rabbit fetuses per 100 implantation sites was similar in control and treated groups. Similar findings were observed in pups from treated and control dams. Examinations of external, internal and skeletal development disclosed no effects which could be related to prenatal exposure of fetuses to the cannabinoids (74, 94).

Although doses used in this experiment are much smaller than those used in previous experiments, they are behaviorally active doses as shown by the observed behavioral changes listed above. When compared to the average oral active dose in man of 500 microgram/kg, the 5-50 mg/kg doses represent 10-100 times the effective human dose.

At high dose level of 200 mg/kg i.p., which is almost 1/2 of the LD_{50} by this route (158), delta-9-THC was shown to significantly increase resorptions in mice especially if administered during early organogenesis, on days 8 and 9 of gestation. The developing organism appears to be less sensitive to toxic effects of delta-9-THC during late organogenesis or the period of fetal maturation (75). In the same study, delta-9-THC also significantly reduced the body weight of the surviving fetuses and this effect was most pronounced when delta-9-THC was administered between days 10 and 13.

In conclusion, the NIMH studies confirm the report of Pace (153) that, at doses 10-100 times the effective human doses, synthetic or natural marihuana does not appear to have serious deleterious effects during pregnancy, on the fetus, the mother, or, after birth, on the newborn.

BEHAVIORAL EFFECTS

This part of the preclinical section will summarize some of the effects of cannabinoids on the behavior of animals reported for the most part in the last two years. The use of animal subjects to study drug-behavior interactions has many advantages. The investigator can know precisely the genetic

and behavioral history of the animals as well as systematically control their behavior. Before going into the experimental results, however, it might be well to point out some important background aspects.

Methodological Considerations

Interpretation of data obtained from behavioral studies of cannabinoids must take into consideration the type of behavior measured (learned or spontaneous) the behavioral tests used, as well as the type of subjects (species and strain) and route of administration. In common with other drugs, it has been shown that the behavioral effects of cannabinoids may be significantly altered by variations in the route of administration and testing situation (123).

During the past year, investigators studying cannabinoid-behavior relationships used paradigms to test both learned and unlearned performance. In contrast to the earlier literature, investigators now use learned tasks more frequently than unlearned tasks to evaluate the effects of marihuana on behavior. This is probably because of the tighter degree of specificity and control available in learned paradigms. General motor performance and open-field activity have been used to characterize unlearned behavior of mice and rats while maze performance has been used extensively to measure simple learned behavior. A number of other operant conditioning techniques have been employed to measure more complex behaviors. Such methods have included the use of simple and multiple schedules of reinforcement baselines, active and passive avoidance paradigms, conditioned emotional response (CER) tests and timing tasks.

The species used to study behavioral effects of cannabinoids have varied from fish, birds, mice and rats to squirrel and rhesus monkeys, chimpanzees and great apes. By far the greatest number of experiments reported in the literature employed rodents as subjects. This choice is based largely upon the economy of rodent laboratories, the efficiency with which mice and rats can be used in group experimental designs, and the wealth of baseline data already available detailing the behavior of rodents in comparable test situations.

During the past year, there has been an upsurge in the use of primates as experimental subjects. Squirrel monkeys, rhesus, macaques, and great apes have been employed to study the effects of cannabinoids. The use of chimpanzees is of particular interest since some of the preclinical data collected on them is quite similar to that reported in clinical studies of human volunteers. The use of primates, while involving greater expenditures can certainly be justified in terms of the data generated, as they provide the opportunity to study the effects of drugs in more complex test situations. In addition, the analysis is usually focused upon the behavior of single individuals, an alternative approach to group designs.

In general, the route of administration varied with the species. In birds (pigeons), administration of cannabinoids was usually by the parenteral (intramuscular) route. In rats, the intraperitoneal (i.p.) route was used in about 90 percent of the studies and the oral route in the remaining ones. Contrary to metabolic studies, for instance, the intravenous (IV) route of administration

was used in only one experiment. Mice were given cannabinoids either i.p. or IV. In primates, the oral (gavage, baited fruit, or smoking) or IV routes were used equally.

This review will describe experimental results derived from a variety of techniques in the following areas: (a) gross behavioral observations, (b) aggression and social competition, (c) avoidance and aversive control, (d) schedules of reinforcement and (e) timing behavior.

Gross Behavioral Observations

Studies in the area of gross behavioral observation can be divided methodologically into two categories, nonsystematic and systematic. Nonsystematic studies, as the name implies, place no restriction on the type or quantification of behavior recorded. Therefore, these studies yield descriptive, unquantitative impressions of an animal's gross behavior under the influence of a drug. In contrast, systematic studies rely upon preplanned scales or measures to record selected aspects of an animal's behavior. Certain patterns or types of behavior are preselected to observe, measure and quantify a drug effect. Despite their underlying methodological difference, both systematic and nonsystematic studies measure unlearned behavior. Of necessity, a full evaluation of the effects of cannabinoids on behavior includes both types of studies. The nonsystematic studies have been often reported and are summarized in the section on pharmacological profile of the cannabinoids. The systematic studies will be considered in more detail.

Systematic studies with cannabinoids have used a number of different parameters to quantitate drug effects. Habituation experiences, vocalization, motor tasks, and open-field behavior have been measured.

Brown (4) reported that mice which received IV doses of delta-8-THC immediately prior to an habituation experience (pre-exposure to a cage where latency to drink would later be measured) did not appear to be significantly different from non-habituated vehicle-treated mice. The results suggest that delta-8-THC inhibited the habituation and may be similar in action to anti-cholinergic drugs (scopalamine, atropine, and ditran). These results indicate that the effects of delta-8-THC may be mediated via an anti-cholinergic mechanism.

Henriksson and Jarbe (79) observed vocalizations of rats when squeezed behind the forelimbs after administration of delta-8- or delta-9-THC via i.p. or oral routes using different vehicles or after inhalation of marihuana smoke. They concluded that vocalization might be a useful indicator of cannabis effects at relatively low doses of the drug. Cohn et al. (23) used a scaled set of motor tasks in addition to vocalization to measure the effect of marihuana extract administered orally to rats. The results showed that drugged rats had significantly higher scores than controls (the drugged animals were more sluggish); with drugged female rats significantly more affected than drugged males. These results indicate the possible role of sex difference in responses to marihuana extract (MED).

In addition to these studies, Masur et al. (129) evaluated the effects of intra-peritoneally administered cannabis extract and delta-9-THC using an open-field technique. Decreases in bolus production, rearing and grooming behaviors were found in the treated rats. However, ambulation was not significantly different from controls. The work of Drew et al. (43) confirms the findings cited above. These investigators measured the effects of intra-peritoneally administered delta-9-THC on behavior or rats in an open-field testing situation. Results indicated that drugged rats exhibited reductions compared to controls in the following behavioral measures: rearing, grooming, sniffing, and bolus production. However, these investigators found that ambulation was reduced, a result which differs from Masur et al. (129).

Aggression and Social Competition

Studies in this area are unique in that the focus of analysis shifts to the interaction between animals. Paradigms used to study aggression can be divided into four categories as follows: predatory, shock induced, starvation induced, isolation induced. With few exceptions, studies of the relationship between cannabis and aggression employ rodents (mice and rats) as the subjects of choice. Two recent studies of aggressive behavior cannot be conveniently included in one of the categories listed above. An experiment by Gonzalez et al. (69) studied the effects of marihuana extract on the aggressive behavior and ritual displays of Siamese fighting fish (Beta splendens). The investigators found that delta-9-THC or cannabis extract decreased the number of fighting episodes between paired males. This reduction in aggressive behavior and the general profile was similar to that reported when the fish were tested under the influence of hypnotic drugs. Display and aggressive behavior of the drugged fish became similar to control subjects after nine consecutive days of treatment with cannabis.

Kilbey et al. (99) evaluated the effects of attack behavior of mice on passive mice in a T maze testing situation after the experimental animals had received intravenous injections of delta-9-THC. The results of the experiment indicated that the drug reduced aggression and agree with the data of Santos et al. (172) who reported that an extract of marihuana reduced isolation induced aggression.

A. Predatory Aggression

The typical behavioral situation observed in this form of aggression is the attack and killing behavior of rodents (rats) when they are presented with a frog or a turtle in their home cage. Kilbey et al. (97) measured the effects of intravenously administered delta-9-THC on frog killing behavior by rats and found a dose related increase in the latency to attack and kill frogs immediately after receiving the drug. In a second study, Kilbey et al. (98) investigated the time course of the drug effect and found that the latencies to kill were longest when measurements were taken 0, 15, and 30 minutes post injection. The peak of the drug effects was found to occur between 0-15 minutes after drug administration. Another study by McDonough et al. (135) investigated the effects of delta-9-THC i.p. (6.4 mg/kg) on the turtle killing behavior of rats. The results of this experiment indicated that the percentages of attacks at 1 and 2 hours post injection were significantly less on drug days. At 4 and 8 hours after drug administration, attack behavior could not be distinguished

from placebo administration. These data are in general agreement with the findings of Kilbey et al. (97) and Kilbey et al. (98), cited above.

B. Shock Induced Aggression

In this paradigm as the name implies, the fighting behavior in pairs of rats is induced via electric shocks that both animals receive while they are in the observation arena. Two sets of studies employed this paradigm to investigate the relationship between aggression and cannabis. Carder and Olsen (8) found significant increases in shock induced fighting if either or both of a pair of rats was administered marihuana extract (MED) intraperitoneally. The increase was found to be dose dependent and occurred at doses of 0.12, 0.25, 0.50 mg/kg; at doses of 1.0 and 2.0 mg/kg fighting behavior was shown to decrease when compared to control animals On the next two days of testing, fighting was not observed to increase at any dose of marihuana. In a subsequent control study these investigators found that familiarization with either the drug or the testing situation was sufficient to prevent the drug from increasing fighting behavior. Manning and Elsmore (124) found that rats given dose levels of delta-9-THC i.p. ranging between 0.64-6.4 mg/kg showed no increase in fighting behavior over control animals. The conflicting results between the two studies may be attributed to the fact that in Manning and Elsmore's study the rats received extensive pre-training in the apparatus before being given the drug. This is just the type of condition which Carder and Olsen's study indicated would preclude drug effects from being observed

C Starvation Induced Aggression

In this paradigm rats are administered intraperitoneal injections of cannabis extract while they are maintained on a food deprivation schedule. The behavior measured is fighting between pairs of rats receiving this treatment regime. Two early papers by Carlini and Masur (10, 11) described the basic experimental situation. Carlini et al. (12) investigated some of the factors that may contribute to starvation-marihuana induced aggression. The results of the study suggested that the stress of hunger is the factor which facilitates the development of aggressive behavior by chronic administration of marihuana. A recent report, however, has described aggressiveness in normally fed rats after receiving cannabinoids for 4 or 5 weeks (3).

Neto and Carlini (149) found that when p-chlorophenylalanine (PCPA) and dihydrophenlalanine (DOPA) were administered separately to food deprived pairs of rats which received marihuana extract, each drug potentiated the fighting behavior. When the drugs were given in combination the potentiation was greater than either of the drugs given alone. The drugs had no effect if the rats were not treated with marihuana or if they were fed ad libitum. Carlini and Gonzalez (13) found that THC given during morphine withdrawal induced aggressiveness in rats so treated but this effect was observed only after 60 days of treatment with morphine. While d-amphetamine was also shown to induce aggression, THC was found to be more efficient in that it induced aggressiveness sooner.

D. Social Competition

A study by Masur et al. (128) found that rats treated with delta-9-THC in a situation where they competed for food won more encounters than those not so treated; when "loser" rats were subsequently treated with the drug in the same testing situation (straight alley) they prevailed over the former "winners." When the testing apparatus was changed from a straight runway to a T maze, those rats given THC were mostly "losers" in the competitive encounters. In a second study Masur et al. (130) showed that rats empirically rated as "losers" became "winners" when treated with 10 mg/kg of cannabis extract prior to a contest in a straight alley food competition test. Masur et al. (131) also showed that when pairs of rats were tested in operant bar pressing situations (VI and CRF schedules were used) that marihuana extract could induce a shift in the social hierarchy and this change is partially dependent upon environmental contingencies. These data support the results of Masur et al. (130, 131) cited above.

Avoidance and Aversion Control

A number of recent studies which employed avoidance paradigms and aversive control were used to study cannabinoid effects.

A. Conditioned Food Aversion

A study by Elsmore and Fletcher (46) investigated the effects of delta-9-THC using a conditioned food aversion paradigm. Rats were administered doses of delta-9-THC either orally or intraperitoneally immediately after drinking a saccharine solution. A subsequent 2-bottle preference test between water and saccharine indicated an inverse relationship between drug dose and saccharine preference. These data suggest that delta-9-THC in doses of 2 mg/kg or above is an aversive substance for rats and that investigators should take into account this fact when interpreting any behavioral effects of the drug. A second study by Elsmore (47) using the conditioned aversion paradigm indicated that little if any of the effect observed is due to the unfamiliarity of the unconditioned stimulus.

B. Acquisition, Retention and Extinction of Avoidance

A study of acquisition and retention of a conditioned emotional response (CER) by Gonzalez et al. (70) indicated that acute administration i.p. of 10 mg/kg of Cannabis extract partially blocked the acquisition of the response. When measured in a retention test, the CER was significantly attenuated by Cannabis extract (10 mg/kg) given either acutely or chronically. These data suggest that cannabis acts on the process underlying acquisition and retention of a CER and thus mimics the action of some CNS depressants (reserpine and chlordiazapoxide) which are able to block CER acquisition

Henriksson and Jarbe (80) studied acquisition of an avoidance response by rats in a shuttle box and found that rats administered delta-9-THC i.p. showed a significantly reduced acquisition of the avoidance response. In

addition results from this study indicated symmetrically state dependent learning under the influence of synthetic cannabinoids. In a series of studies using several avoidance paradigms Robichaud et al. (168) found that delta-9-THC given i.p. to mice reduced avoidance responding in some test situations but not others. In addition he found that delta-9-THC did not appear to generally inhibit acquisition of a CER. A study by Kubena and Barry (106) found that rats were able to use drugged (delta-1-THC) and undrugged states as discriminative stimuli for approach and avoidance behavior. A study by Jaffe and Baum (90) found that rats which received hashish and were tested in an avoidance task made significantly more extinction and spontaneous recovery responses than controls. Such data indicate that Cannabis may interfere with the inhibition process in extinction.

C. Avoidance and Tolerance Effects

Harris et al. (77a) studied the effects of IV doses of delta-9-THC on discriminated avoidance performance of rhesus monkeys and found that the monkeys exhibited an increase in shocks received but a rapid tolerance to the drug developed by the third and fourth session respectively for the two monkeys tested. Krasnegor and Elsmore (103) studied Sidman avoidance in rhesus monkeys and found a positive relationship between dose of delta-9-THC and total shocks on day 1 and an inverse relationship between drug dose and response rate on day 1. By day seven at each dose studied both monkeys showed a return to control levels on both dependent variables indicating the possible development of tolerance to the effects of the drug.

Schedules of Reinforcement

The schedules of reinforcement used to study the effects of cannabis included: fixed ratio (FR); fixed interval (FI); variable interval (VI); and time out (TO). These schedules were studied separately and as components of multiple schedules. Rats, pigeons, monkeys, and chimpanzees were used as experimental subjects. The literature supports the generalization that FR responding is markedly reduced by Cannabis. Studies by Henriksson and Jarbe (79), Pradhan, Bailey, and Ghosh (163), Peterson et al. (157) and Frankenheim et al. (55) all reported reduced responding in their subjects in experiments where the responding of the animals was controlled by fixed ratio schedules of reinforcement. Similar results were reported by Frankenheim et al. (55) and Krasnegor (104) who studies the effects of Cannabis on fixed ratio responding in pigeons. In primates, Harris et al. (77a) reported that the monkeys in his study showed a marked reduction in FR responding after intravenous administrations of delta-9-THC. In chimpanzees however Ferraro et al. (48) reported that cannabis had a variable effect on fixed ratio responding. In addition both Ferraro and Billings (49) and Pradhan et al. (163) reported that post-reinforcement time was affected by the drug.

Responding on fixed interval reinforcement schedules was also found to be substantially reduced under the influence of Cannabis. In studies using both rats and pigeons, Manning and Elsmore (124), and Frankenheim et al. (55) showed that cannabis reduced responding controlled by fixed interval schedules of reinforcement.

D. Social Competition

A study by Masur et al. (128) found that rats treated with delta-9-THC in a situation where they competed for food won more encounters than those not so treated; when "loser" rats were subsequently treated with the drug in the same testing situation (straight alley) they prevailed over the former "winners." When the testing apparatus was changed from a straight runway to a T maze, those rats given THC were mostly "losers" in the competitive encounters. In a second study Masur et al. (130) showed that rats empirically rated as "losers" became "winners" when treated with 10 mg/kg of cannabis extract prior to a contest in a straight alley food competition test. Masur et al. (131) also showed that when pairs of rats were tested in operant bar pressing situations (VI and CRF schedules were used) that marihuana extract could induce a shift in the social hierarchy and this change is partially dependent upon environmental contingencies. These data support the results of Masur et al. (130, 131) cited above.

Avoidance and Aversion Control

A number of recent studies which employed avoidance paradigms and aversive control were used to study cannabinoid effects.

A. Conditioned Food Aversion

A study by Elsmore and Fletcher (46) investigated the effects of delta-9-THC using a conditioned food aversion paradigm. Rats were administered doses of delta-9-THC either orally or intraperitoneally immediately after drinking a saccharine solution. A subsequent 2-bottle preference test between water and saccharine indicated an inverse relationship between drug dose and saccharine preference. These data suggest that delta-9-THC in doses of 2 mg/kg or above is an aversive substance for rats and that investigators should take into account this fact when interpreting any behavioral effects of the drug. A second study by Elsmore (47) using the conditioned aversion paradigm indicated that little if any of the effect observed is due to the unfamiliarity of the unconditioned stimulus.

B. Acquisition, Retention and Extinction of Avoidance

A study of acquisition and retention of a conditioned emotional response (CER) by Gonzalez et al. (70) indicated that acute administration i.p. of 10 mg/kg of Cannabis extract partially blocked the acquisition of the response. When measured in a retention test, the CER was significantly attenuated by Cannabis extract (10 mg/kg) given either acutely or chronically. These data suggest that cannabis acts on the process underlying acquisition and retention of a CER and thus mimics the action of some CNS depressants (reserpine and chlordiazapoxide) which are able to block CER acquisition

Henriksson and Jarbe (80) studied acquisition of an avoidance response by rats in a shuttle box and found that rats administered delta-9-THC i.p. showed a significantly reduced acquisition of the avoidance response. In

addition results from this study indicated symmetrically state dependent learning under the influence of synthetic cannabinoids. In a series of studies using several avoidance paradigms Robichaud et al. (168) found that delta-9-THC given i.p. to mice reduced avoidance responding in some test situations but not others. In addition he found that delta-9-THC did not appear to generally inhibit acquisition of a CER. A study by Kubena and Barry (106) found that rats were able to use drugged (delta-1-THC) and undrugged states as discriminative stimuli for approach and avoidance behavior. A study by Jaffe and Baum (90) found that rats which received hashish and were tested in an avoidance task made significantly more extinction and spontaneous recovery responses than controls. Such data indicate that Cannabis may interfere with the inhibition process in extinction.

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Responding on variable interval (VI) schedules was reported to be reduced at high doses of Cannabis (12-18 mg/kg and 25 mg/kg). Thus both Grisham and Ferraro (73a) and Carlini (9) reported complete suppression of variable interval responding of rats after high doses were administered i.p. At low doses of the drug conflicting data were reported. Grisham and Ferraro (73a) indicated that at doses of 0.25-8.0 mg/kg, variable interval responding was facilitated in rats, while Masur et al. (131) reported that rats in their experiment showed a decrease in VI responding at comparable low dose levels. This discrepancy may be partially due to the different forms of cannabis used in the two studies.

Responding in the time out phases of multiple schedules was found to be unaffected by administration of delta-9-THC Ferraro et al. (48) and Ferraro and Billings (49).

Timing Behavior

Timing behavior was studied in both rodents (rats) and great apes (chimpanzees and orangutan) using a schedule of responding known as differential reinforcement of low rates of responding (DRL). In all the animals studied the drug produced an increase in the frequency of short interresponse times (IRT's). Pradhan et al. (162) found that delta-9-THC increased overall response rate in rats responding on a DRL schedule for food. At low doses of the drug (5 mg/kg and below) an increase in the frequency of shorter IRT's was observed. A similar finding was reported by Cole et al. (24) who studied the DRL performance of chimpanzees and an orangutan. A slight shift to shorter IRT's was reported to occur after the animals smoked cigarettes containing delta-9-THC. A dose related shift to shorter IRT's was also reported by Conrad et al. (25) in three chimpanzees after the animals received oral doses of delta-9-THC. Effects of the drug were reported at dose levels (0.25 mg/kg) that produce deficits in performance of human volunteers after they smoked cigarettes containing marihuana. Two additional studies, Ferraro et al. (48) and Ferraro and Billings (49) reported a shift in responding to shorter IRT's in chimpanzees which responded on a DRL controlled schedule of reinforcement.

Data of the type reported above must be interpreted cautiously. Although one may be tempted to speculate that a drug induced increase in shorter IRT's may be indicative of over estimation of temporal intervals, one should also be cognizant of the fact that the drug in the doses studied has a general facilitatory effect on responding in the DRL situation. Thus, at least in several of the studies cited, there was an overall drug induced increase in responding. Such an effect would have the net result of increasing the total number of short IRT's but would not necessarily be indicative of a timing deficit.

Implications and General Conclusions

Great care must be exercised in generalizing preclinical behavioral results to humans. Using this caution as a guide we shall attempt to relate some of the results from the animal studies reviewed to the clinical literature of marihuana research.

In addition to reductions in gross behavioral indices, the literature also supports the conclusion that food reinforced scheduled controlled performance is depressed under the influence of the drug. Thus across species, routes of administration, dose levels, and forms of cannabis, it was found that fixed ratio responding was depressed or almost suppressed to a near zero rate. Similar results were found for responding controlled by fixed interval schedules of reinforcement.

These results may relate to two clinical studies of marihuana smoking and work in human volunteers. A study of smoking and operant performance undertaken by the Marihuana Commission (Mendelson et al.)(139) indicated that when casual and heavy users of the drug were allowed to work to obtain marihuana cigarettes no difference was seen in their performance. Subjects earned the maximum number of points available throughout the drug period and showed no consistent change in their working patterns that could be systematically related to marihuana. In contrast to these results, the preliminary findings of the Le Dain Commission study (6) indicated when human volunteers were required to consume large doses of marihuana after long periods of abstinence, work performance tended to become depressed. When the group required to consume high doses of marihuana was compared on its work output to a group which consumed only the amounts of the drug that they desired, the forced group showed a dramatic reduction in average productivity. Thus the two studies agree that when subjects are allowed to choose how much of the drug they will consume, no demonstrable changes in work performance was noted. However, when the subjects were forced to consume large quantities of the drug, decrements were observed. This finding is possibly related to the preclinical findings cited above and may suggest that when the dose of the drug is not under the control of the subject or above the level that would be self-administered on an ad libitum basis that marihuana has a suppressive effect on behavior.

A second finding of interest was the fact that the drug itself under certain circumstances may be aversive. Thus two studies support the conclusion that delta-9-tetrahydrocannabinol when administered either orally or intraperitoneally produced a conditioned food aversion in rodents. Such data should serve as a reminder for experimenters that they must take into account the possible aversive effects of the drug when making interpretations of behavioral results. These preclinical findings are of interest also because preliminary data from the Le Dain (6) study indicate that human volunteers found cannabis to be aversive when they were forced to consume large doses of it for long periods of time. The subjects reported the drug was subjectively unpleasant and in the highest dose condition studied, most subjects requested to stop using the drug. The drug was so unpleasant for some that they indicated they would no longer participate in the study if forced to continue smoking the high doses required.

The data on timing performance indicate that the drug does have an effect on spaced responding. Thus both rodents and primates show a shift in inter-response times (IRT) on a schedule termed differential reinforcement of low rate of responding (DRL). As was indicated above, such data, although they are suggestive of timing deficits reported in human studies, must be dealt with cautiously. However, one study in particular Conrad et al. (25) is suggestive of a timing change. The study is important for two reasons. First, it was able to demonstrate alterations in spaced responding at dose levels of delta-9-tetrahydrocannabinol that are well within the range of psychoactivity reported for humans. Second, the study suggests that chimpanzees may be the animals of choice to study certain effects of marihuana (e.g., timing and chronic behavioral effects), and that the results of such studies may be generalized to man.

Since there is a lack of clinical data relating the effects of marihuana to human aggression, it would be unwarranted to speculate about this drug-behavior relationship. The only clinical reports on this problem are some preliminary results from the Le Dain (6) Commission where the investigators reported that the: .. "drug did not seem to induce hostility or aggression, and no evidence was found of social deterioration..."

In summary, a good deal of the animal behavioral data correlates well with clinical investigations of the behavioral effects of marihuana in man and thus substantiates the predictive and confirmatory value of preclinical behavioral analysis of cannabis.

References

1. Adams, P.M. and Barratt, E.S. The effects of a marihuana extract on the general motor activity of the squirrel monkey. Psychonomic Sciences, 25(5):279-280, 1971.

2. Bose, G.C., Saifi, A.Q. and Bhagwat, A.W. Studies on Pharmacological actions of Cannabis indica. Part III. Archives Internationales de Pharmacodynamie et de Therapie, 147:291-297, 1964.

3. Braude, M.C. Toxicology of cannabinoids. Ciba Symposium, Oxford Press, 1972 (in press).

4. Brown, H. Some anticholinergic-like behavioral effects on trans (-) Delta-8-tetrahydrocannabinol. Psychopharmacologia, 21:294-301, 1971.

5. Burstein, S., Rosenfeld, J. and Wittstrick. Isolation and characterization of two major metabolites of Delta-1-tetrahydrocannabinol. Science, 176:422-423, 1972.

6. Cannabis. A report on the commission of inquiry into the non-medical use of drugs. 149-151, 1972.

7. Cappell, H., Webster, C.D., Herring, B.S. and Ginsberg, R. Alcohol and marihuana: a comparison of effects on a temporally controlled operant in humans. Journal of Pharmacology and Experimental Therapeutics. 182:195-203, 1972.

8. Carder, B. and Olsen, J. Marihuana and shock induced aggression in rats. Physiology and Behavior, 8:599-602, April 1972.

9. Carlini, E.A. Tolerance to chronic administration of Cannabis sativa (marihuana) in rats. Pharmacology, 1:135-142, 1968.

10. Carlini, E.A. and Masur, J. Development of aggressive behavior in rats by chronic administration of Cannabis sativa. Life Sciences, 8:607-620, 1969.

11. Carlini, E.A. and Masur, J. Development of fighting behavior in starved rats by chronic administration of (-)-Delta-9-trans-tetrahydrocannabinol and Cannabis extract. Communications in Behavioral Biology, 5:57-61, 1970.

12. Carlini, E.A., Hamaoui, A. and Martz, R.M. Factors influencing the aggressiveness èlicited by marihuana in food-deprived rats. British Journal of Pharmacology and Chemotherapy, 44:794-804, April 1972.

13. Carlini, E.A. and Gonzales, C. Aggressive behavior induced by marihuana compounds and amphetamine in rats previously made dependent on morphine. Experientia, 28:542-544, 15 May 1972.

14. Cavero, I., Buckley, J.P. and Jandhyala, B.S. Parasympatholytic activity of (-)-Delta-9-trans-tetrahydrocannabinol in mongrel dogs. European Journal of Pharmacology, 19(2):301-304, 1972.

15. Cavero, I., Kubena, R.K., Dziak, J., Buckley, J.P. and Jandhyala, B.S. Certain observations on interrelationships between respiratory and cardiovascular effects of (-)-Delta-9-trans-tetrahydrocannabinol. Research Communications in Chemical Pathology and Pharmacology, 3(3):483-492, 1972.

16. Chari-Bitron, A. Stabilization of rat erythrocyte membrane by Delta-1-tetrahydrocannabinol. Life Sciences, 10:1273-1279, 1971.

17. Chari-Bitron, A. and Bino, T. Effect of Delta-1-tetrahydrocannabinol on ATPase activity of rat liver mitrochondria. Biochemical Pharmacology, 20(2):473-475, 1971.

18. Chopra, R.N. and Chopra, G.S. The present position of hemp drug addiction in India. Indian Medical Research Memoirs, 31:1-119, 1939.

19. Christensen, C.W., Best, J.B. and Herin, R.A. Changes seen in the electroencephalogram and heart rate in the rat after administration of marihuana. Federation Proceedings, 30(2):375, 1971.

20. Christensen, C.W., Best, J.B. and Herin, R.A. Effects of Delta-9-tetrahydrocannabinol on limbic electrical activity and heart rate in the rat. Proceedings of the 8th Annual Rocky Mountain Bioengineering Symposium, 163-168, 1971.

21. Christensen, C.W., Freudenthal, R.I., Gidley, J.T., Rosenfeld, R., Biegli, G., Testino, L., Brine, D.R., Pitt, C.G. and Wall, M.E. Activity of Delta-8 and Delta-9-tetrahydrocannabinol and related compounds in the mouse. Science, 172(3979):165-167, 1971.

22. Cohn, R.A., Barratt, E. and Pirch, J.H. Effects of alteration of hormonal balance on responses to marihuana extract. Presented to the Fifth International Congress of Pharmacology, July 23-28, 1972.

23. Cohn, R.A., Barnes, P.S., Barratt, E. and Pirch, J.H. Sex differences in response to marihuana in the rat. Drug Addiction: Experimental Pharmacology, 1:227-234, 1972.

24. Cole, J.M., Pieper, W. and Rumbaugh, D.M. Effects of Delta-9-tetrahydrocannabinol on spaced responding in great apes. Behavioral Biology, 6:285-293, 1971.

25. Conrad, D.G., Elsmore, T.F. and Sodetz, F.J. Delta-9-tetrahydrocannabinol: dose-related effects on timing behavior in chimpanzee. Science, 175:547-550, Feb. 4, 1972.

26. Constantinidis, J. and Miras, C.J. Effect of hashish smoke sublimate on hypothalamic noradrenaline studied by the fluorescence method. Psychopharmacologia, 22(1):80-90, 1971.

27. Contract Report (HSM-42-71-79). Irritation study in rabbit for evaluating subcutaneous administration of Delta-9-THC for 28 consecutive days. Report of September 13, 1971.

28. Contract Report (HSM-42-71-79). Toxicological manifestations in Fischer rats treated orally with Delta-9-tetrahydrocannabinol at doses equivalent to American marihuana and hashish for 28 consecutive days. Report of September 29, 1972.

29. Cottrell, J.C., Sohn, S.S. and Vogel, W.H. Toxic effects of marihuana tar on mouse. Nature, 1972 (in press).

30. Couselinis, A. and Miras, C. The effects of the smoking process on cannabinols. Journal of Forensic Medicine, 18:108-113, 1971.

31. Crisham, M.G. and Ferraro, D.P. Biphasic effects of Delta-9-tetrahydrocannabinol on variable interval schedule performance in rats. Submitted for publication.

32. Davis, W.M., Moreton, J.E., King, W.T. and Pace, H.B. Marihuana on locomotor activity: biphasic effect and tolerance development. Research Communications in Chemical Pathology and Pharmacology, 3(1):29-35, 1972.

33. Deneau, G.A. and Kaymakcalan, S. Physiological and psychological dependence to synthetic Delta-9-tetrahydrocannabinol (THC) in Rhesus monkeys. Pharmacologist, 13:246, 1971.

34. DeRopp, R.S., Kastl, L.H. and Balbus, L. Acute effects of marihuana smoke on mice. Proceedings of the Western Pharmacology Society, 15:21-24, 1972.

35. Dewey, W.L., Harris, L.S. and Kennedy, J.S. Some pharmacological and toxicological effects of l-trans-8 and l-trans-9-tetrahydrocannabinol in laboratory rodents. Archives Internationales de Pharmacodynamie et de Therapie, 196:133-145, 1972.

36. Dewey, W.L., Jenkins, J., O'Rourke, T. and Harris, L.S. The effects of chronic administration of trans-Delta-9-tetrahydrocannabinol on behavior and the cardiovascular system of dogs. Archives Internationales de Pharmacodynamie et de Therapie, 197:262-275, 1972.

37. Dewey, W.L., Peng, T.C. and Harris, L.S. The effect of L-trans-Delta-9-tetrahydrocannabinol (Delta-9-THC) on the hypothalamo-hypophysela-adrenal axis of rats. Pharmacologist, 12:259, 1970.

38. Dewey, W.L. and Turk, R.F. The excretion and metabolism of ^{3}H-Delta-9-THC in intact and bile duct cannulated rats. Federation Proceedings, 31:506 Abs, 1972.

39. Dewey, W.L., Yonce, L.R., Harris, L.S., Reavis, W.M., Griffin, E.D.J. and Newby, V.E. Some cardiovascular effects of trans-Delta-9-tetrahydrocannabinol (Delta-9-THC). Pharmacologist, 12:259, 1970.

40. deZeeuw, R.A., Malingre, T.M. and Merkus, F.W.H.M. Delta-1-tetrahydrocannabinolic acid, an important component in the evaluation of cannabis products. Journal of Pharmacy and Pharmacology, 24:1-6, 1972.

41. Domino, E.F. Neurophycopharmacologic studies of marihuana: some synthetic and natural THC derivatives in animals and man. Annals of the New York Academy of Sciences, 191:166-191, 1971.

42. Domino, E.F., Hardman, H.F. and Seevers, M.H. Central nervous system actions of some synthetic tetrahydrocannabinol derivatives. Pharmacological Reviews, 23:317-336, 1971.

43. Drew, W.G., Miller, L.L. and Wikler, A. Effect of Delta-9-tetrahydrocannabinol on the open-field activity of the rat. Psychopharmacologia, 23(3):289-299, 1972.

44. Durandina, A.I. and Romasenko, V.A. Functional and morphological disorders in chronic poisoning by resinous substance from Yujnochuisk Cannabis resin (Part 2). Bulletin on Narcotics, 24(1):31-37, 1972 (January-March).

45. Eaton, B.J., Hartowicz, L.W., Latta, R.P., Knutson, H., Paulsen, A. and Eshbaugh, R. Controlling Wild Hemp. Agricultural Experiment Station, Kansas State University of Agricultural and Applied Science, Manhattan, Kansas, Report of Progress, 1972.

46. Elsmore, T.F. and Fletcher, G.V. Delta-9-tetrahydrocannabinol: aversive effects in rat at high doses. Science, 175:911-912, 25 Feb 1972.

47. Elsmore, T.G. Saccharine aversion induced by Delta-9-THC: effects of repeated doses prior to pairing with saccharine. Proceedings 80th Annual Convention of the American Psychological Association, 80:817-818, Sept.1972.

48. Ferraro, D.P., Grilly, D.M. and Lynch, W.C. Effects of marihuana extract on the operant behavior of chimpanzees. Psychopharmacologia, 22(4):333-351, 1971.

49. Ferraro, D.P. and Billings, D.K. Comparison of behavioral effects of synthetic (-)-9-trans-tetrahydrocannabinol and marihuana extract distillate in chimpanzees. Psychopharmacologia, 25:169-174, 1972.

50. Fetterman, P.S. and Turner, C.E. Constituents of Cannabis sativa L. propyl homologs of cannabinoids from an Indian variant. Journal of Pharmaceutical Sciences, 61:1476-1477, 1972

51. Ford, R.D. and McMillan, D.E. Further studies on the behavioral pharmacology of 1-Delta-8 and 1-Delta-9-tetrahydrocannabinol. Federation Proceedings, 31(2):506 Abs., 1972.

52. Forney, R.B. and Kiplinger, G.F. Toxicology and pharmacology of marihuana. Annals of the New York Academy of Sciences, 191:74-82, 1971.

53. Forney, R.B. Toxicology of marihuana. Pharmacological Reviews, 23(4):279-284, 1971.

54. Forrest, I.S., Green, D.E., Rose, S.D., Skinner, G.C. and Torres, D.M. Fluorescent-labeled cannabinoids. Research Communications in Chemical Pathology and Pharmacology, 2:787-792, 1971.

55. Frankenheim, J.M., McMillan, D.E. and Harris, L.S. Effects of L-Delta-9 and L-Delta-8-trans-tetrahydrocannabinol and cannabinol on schedule-controlled behavior of pigeons and rats. Journal of Pharmacology and Experimental Therapeutics, 178(1):241-252, 1971.

56. Freudenthal, R.I., Martin, J. and Wall, M.E. Distribution of Delta-9-tetrahydrocannabinol in the mouse. British Journal of Pharmacology and Chemotherapy, 44:244-249, 1972.

57. Friedman, E. and Gershon, S. Delta-9-tetrahydrocannabinol (Delta-9-THC): cerebral dopamine (DA) metabolism and behavioral effects after acute and chronic treatment in rats. Presented at the 5th International Congress on Pharmacology, San Francisco, July 23-28, 1972.

58. Fujimoto, M., Trusty, D.M. and Himwich, H.E. Electroencephalographic analysis of Delta-9-trans-tetrahydrocannabinol in the rabbit. Federation Proceedings 31:Abstract, 1972.

59. Fuxe, K. and Jonsson, G. The effect of tetrahydrocannabinols on central monamine neurons. Acta Pharmaceutica Suecica, 8(6):695, 1971.

60. Gallager, D.W., Sanders-Bush, E. and Sulser, F. Dissociation between behavioral effects and changes in metabolism of cerebral serotonin (5-HT) following Delta-9-tetrahydrocannabinol. Pharmacologist, 13(2): 296, 1971.

61. Garattini, A. Effects of a Cannabis extract on gross behavior. In Hashish: Its Chemistry and Pharmacology, ed. by S.G. Wolstenholme and J. Knight, pp. 70-82, Little, Brown Co., Boston, 1965.

62. Garriott, J.C., Forney, R.B., Hughes, E.W. and Richards, A.B. Pharmacologic properties of some Cannabis related compounds. Archives Internationales de Pharmacodynamie et de Therapie, 171:1425-1434, 1968.

63. Garriott, J.C., King, L.J., Forney, R.B. and Hughes, F.W. Effects of some tetrahydrocannabinols on hexobarbital sleeping time and amphetamine induced hyperactivity in mice. Life Sciences, 6(9):2119-2128, 1967.

64. Gerber, W. and Schramm, L. Teratogenicity of marihuana extract as influenced by plant origin and seasonal variation. Archives Internationales de Pharmacodynamie et de Therapie, 177(1):224-230, 1969.

65. Gerber, W.F. Effect of marihuana extract on fetal hamsters and rabbits. Toxicology and Applied Pharmacology, 14:276-282, 1969.

66. Gill, E.W. and Jones, G. Nonexchange synthesis of tritium-labeled tetrahydrocannabinols. Journal of Labelled Compounds 8:237-248, 1972.

67. Gill, E.W. and Jones, G. Brain levels of Delta-1-tetrahydrocannabinol and its metabolites in mice -- correlation with behavior and the effect of the metabolic inhibitors SKF 525A and piperonyl butoxide. Biochemical Pharmacology 21:2237-2248, 1972.

68. Goldstein, F.J. Marihuana--a pharmacological profile. American Journal of Pharmacy, 143(2):59-65, 1971.

69. Gonzalez, S.C., Matsudo, V.K.R. and Carlini, E.A. Effects of marihuana compounds on the fighting behavior of Siamese fighting fish (Betta splendens). Pharmacology, 6:186-190, 1971.

70. Gonzalez, S.C., Karniol, I.G.and Carlini, E.L. Effects of Cannabis sativa on conditioned fear. Behavioral Biology, 7:83-94, Feb 1972.

71. Grant, J.D., Gross, S.J., Lomax, P. and Wong, R. Antibody detection of marihuana. Nature New Biology 236:216-217, 1972.

72. Green, D.E. Automated detection of abused drugs by direct mass fragmentometry. Proceedings of the Western Pharmacology Society, 15:74-77, 1972.

73. Greene, M.L. and Saunders, D.R. Metabolism of tetrahydrocannabinol by the small intestine. Journal of Clinical Investigations (in press).

73a Grisham, M.G. and Ferraro, D.A. Biphasic effects of Delta-9-tetrahydrocannabinol on variable interval schedule performance in rats. Submitted for publication

74. Haley, S.L., Wright, P.L., Plank, J.B., Keplinger, M.L., Braude, M.C. and Calandra, J.C. The effect of natural and synthetic Delta-9-tetrahydrocannabinol on fetal development. Toxicology and Applied Pharmacology, 1973 (in press).

75. Harbison, R.D. and Mantilla-Plata, B. Prenatal toxicity, maternal distribution and placental transfer of THC. Journal of Pharmacology and Experimental Therapeutics, 180(2):446-452, 1972.

76. Harris, L.S. General and behavioral pharmacology. Pharmacological Reviews, 23:285-294, 1971.

77. Harris, R.T. 1972, personal communication.

77a. Harris, R.T., Waters, W. and McLendon, D. Behavioral effects in Rhesus monkeys of repeated intravenous doses of Delta-9-tetrahydrocannabinol. Psychopharmacologia, 26:297-306, 1972.

78. Heath, R.G. Marihuana: effects on deep and surface electroencephalograms of man and Rhesus monkeys. (private communication) 1971.

79. Henriksson, B.G. and Jarbe, T. Cannabis induced vocalization in the rat. Journal of Pharmacy and Pharmacology, 23:457-458, 1971.

80. Henriksson, B.G. and Jarbe, T. Effect of two tetrahydrocannabinols (Delta-9-THC and Delta-8-THC) on conditioned avoidance learnings in rats and its transfer to normal state conditions. Psychopharmacologia, 22(1):23-30, 1971.

81. Ho,B.T., An, R., Fritchie, G.E., Englert, L.F., McIsaac, W.M., MacKay, B. and Ho., D.N. Marihuana: some pharmacological studies. Journal of Pharmaceutical Sciences, 60:1761-1764, 1971.

82. Ho, B.T., Taylor, D., Englert, L.F. and McIsaac, W.M. Neurochemical effects of L-Delta-9-tetrahydrocannabinol in rats following repeated inhalation. Brain Research, 31(1):233-236, 1971.

83. Ho, B.T., Estevez, V., Englert, L.F., and McIsaac, W.M. Delta-9-tetrahydrocannabinol and its metabolites in monkey brain. Journal of Pharmacy and Pharmacology, 24:414-416, 1972.

84. Ho, B.T., Taylor, D., Fritchie, G.E., Englert, L.F. and McIsaac, W.M. Neuropharmacological study of Delta-9 and Delta-8-L-tetrahydrocannabinols in monkeys and mice. Brain Research, 38:163-170, 10 Mar 1972.

85. Hockman, C.H. et. al. Electroencephalographic and behavioral alterations produced by Delta-1-THC. Science, 172:968-970, 28 May 1971.

86. Hoffman, N.E. and Kuo-howyang, R. Gas chromatography of Delta-1-tetrahydrocannabinol. Analytical Letters, 5:7-11, 1972.

87. Hollister, L.E., Kanter, S.L., Moore, F. and Green, D.E. Marihuana metabolites in urine of man. Clinical Pharmacology and Therapeutics, 13:849-855, 1972.

88. Holtzman, D., Lovell, R.A., Jaffe, J.H. and Freedman, D.X. 1-Delta-9-tetrahydrocannabinol: neurochemical and behavioral effects in the mouse. Science, 163(3874):1464-1467, 1969.

89. Hosko, J.J. and Hardman, H.F. Effect of Delta-9-tetrahydrocannabinol on cardiovascular responses to stimulation of vasopressor loci in the neuraxis of anesthetized cats. Pharmacologist 13(2):296, 1971.

90. Jaffe, P.G. and Baum, M. Increased resistance-to-extinction of an avoidance response in rats following the administration of hashish resin. Psychopharmacologia, 20:97-102, 1971.

91. Jakubovic, A. and McGeer, P.L. Inhibition of rat brain protein and nucleic acid synthesis by cannabinoids in vitro. Canadian Journal of Biochemistry, 50:654-662, 1972.

92. Jones, R.T. and Stone, G.C. Psychological studies of marihuana and alcohol in man. Psychopharmacologia, 18:108-117, 1972.

93. Kaymakcalan, S. and Deneau, G.A. Some pharmacological properties of synthetic Delta-9-tetrahydrocannabinol (THC). Pharmacologist, 13:147, 1971.

94. Keplinger, M.L., Wright, P.L., Haley, S.L., Plank, J.B., Braude, M.C. and Calandra, J.C. The effect of natural and synthetic Delta-9-THC on reproductive and lactation performance in albino rats. Toxicology and Applied Pharmacology 1973, (in press).

95. Kennedy, J.S. Dissertation, University of North Carolina, 1971.

96. Kennedy, J.S. and Waddell, W.J. Whole-body autoradiography of the pregnant mouse after administration of ^{14}C-Delta-9-THC. Toxicology and Applied Pharmacology, 22:252-258, 1972.

97. Kilbey, M.M., Harris, R.T. and Moore, J.W., Jr. Increased latency of frog-killing behavior in the rat following administration of Delta-9-tetrahydrocannabinol. In Reported to the Committee on Problems of Drug Dependence, National Academy of Sciences, Division of Medical Sciences, National Research Council, II:1831-1840, 1971.

98. Kilbey, M.M., Farmer, R. and McLendon, D. Time course of Delta-9-tetrahydrocannabinol inhibition of frog-killing behavior in the rat. Presented at the 19th Annual Convention of the Southwestern Psychological Association, Oklahoma City, Oklahoma, 1972.

99. Kilbey, M.M., Fritchie, C.E. and McLendon, D.M. Attack behavior in mice inhibited by Delta-9-THC. Nature, 283:463-465, 1972.

100. Killam, K.F. and Killam, E.K. The action of tetrahydrocannabinol on EEG and photomyoclinic seizures in the baboon. Presented at the 5th International Congress of Pharmacology, Abstract 744, July 23-28, 1972.

101. Klausner, H.A. and Dingell, J.V. The metabolism and excretion of Delta-9-tetrahydrocannabinol in the rat. Life Sciences, 10:49, 1971.

102. Krantz, J.C. Jr., Berger, H.F. and Welch, B.L. Blockade of (-)-trans-Delta-9-tetrahydrocannabinol depressant effect by cannabinol in mice. American Journal of Pharmacy, 143(5):149-152, 1971.

103. Krasnegor, N.A. and Elsmore , T. Effects of chronic administration of Delta-9-THC an sidman avoidance performance in rhesus monkeys. Proceedings 80th Annual Convention American Psychological Association, 80:819-820, Sept. 1972.

104. Krasnegor, N.A. The effects of Delta-9-THC on auditory discrimination performance in the pigeon. Presented at the Eastern Psychological Association Meeting (Boston), 1972.

105. Kreuz, D.C. and Axelrod, J. Delta-9-tetrahydrocannabinol: localization in body fat. Science (in press)

106. Kubena, R.K. and Barry, H. III. Stimulus characteristics of marihuana components. Nature 235(5338):397-398, 1972.

107. Kubena, R.K., Cavero, I., Jandhvala, B.S. and Buckley, J.P. Certain respiratory and cardiovascular effects of Delta-9-THC in dogs. Pharmacologist, 13(2):247, 1971.

108. Kubena, R.K., Perhach, J.L. and Barry, H. III. Corticosterone elevation mediated centrally by Delta-1-tetrahydrocannabinol in rats. European Journal of Pharmacology, 14:89-92, 1971.

109. Lahiri, P.K., Laddu, A.R. and Hardman, H.F. Effect of Delta-9-tetrahydrocannabinol (THC) on the heart rate (HR) of the dog. Federation Proceedings, 31(2):505 Abs., 1972.

110. Latta, R.P. and Eaton, B.J. Cannabinoid content of Kansas marihuana. Journal of Pharmaceutical Sciences, (in press).

111. Lemberger, L., Crabtree, R.E. and Rowe, H.M. 11-hydroxy-Delta-9-tetrahydrocannabinol: pharmacology, disposition, and metabolism of a major metabolite of marihuana in man. Science, 177:62-64, 1972.

111a Lemberger, L., Weiss, J.L., Watanabe, A.M., Galanter, I.M., Wyatt, R.J. and Cardon, P.V. Delta-9-tetrahydrocannabinol, temporal correlation of the psychological effects and blood levels after various routes of administration. New England Journal of Medicine, 286:685-688, 1972.

112. Leonard, B.E. and Tonge, S.R. The effect of some hallucinogenic drugs upon the metabolism of noradrenaline. Life Sciences, 8(1): 815-825, 1969.

113. Leonard, B.E. The effect of 1,6-tetrahydrocannabinol on biogenic amines and their amino acid precursors in the rat brain. Research Communications in Chemical Pathology and Pharmacology, 3(2):139-145, 1971.

114. Leonard, B.E. and Tonge, S.R. The effects of some hallucinogenic drugs on the metabolism of 5-hydroxytryptamine in the brain. Life Sciences, 8:805-814, 1969.

115. Leuchtenberger, D. and Leuchtenberger, R. Morphological and cytochemical effects of marihuana cigarette smoke on epithelioid cells of lung explants from mice. Nature, 234:227-229, Nov. 26, 1971.

116. Liebman, A.A., Malarek, D.H., Dorsky, A.M. and Kaegi, H.H. Synthesis of olivetol-4,6-$^{14}C_2$, and its conversion to (-)-Delta-9-6a,10a-trans-tetrahydrocannabinol-2,4-$^{14}C_2$ via (-)-Delta-8-6a,10a-trans-tetrahydrocannabinol-2,4-$^{14}C_2$. Journal of Labelled Compounds, 7:241-246, 1971.

117. Lipparini, F., Decarolis, A. and Longo, V.A. Neuropharmacological investigation of some tetrahydrocannabinol derivatives. Physiology and Behavior 4(4):527-532, 1969.

118. Loewe, S. Studies on the pharmacology and acute toxicity of compounds with marihuana activity. Journal of Pharmacology and Experimental Therapeutics, 88:154-161, 1946.

119. Lomax, P. and Campbell, C. Phenitrone and marihuana induced hypothermia. Experientia, 27(10):1191-1192, 1972

120. Loscalzo, B. Effects of hashish (alcoholic extract) on the hypothalamo-hypophysealadrenal axis of the rat. Presented at the Fifth International Congress of Pharmacology, San Francisco, July 23-28, 1972.

121. Magus, R.D. and Harris, L.S. Carcinogenic potential of marihuana smoke condensate. Federation Proceedings, 30:279, 1971.

122. Maitre, L. Effects of some cannabinols on biosynthesis of brain amines and on pituitary response in the rat. Acta Pharmaceutica Suecica, 8(6):693-694, 1971.

123. Manning, F.J., McDonough, J.H., Elsmore, T.F., Saller, C.L. and Sodetz, F.J. Inhibition of normal growth by chronic administration of Delta-9-tetrahydrocannabinol. Science, 174:424-426, 1971.

124. Manning, F.J. and Elsmore, T.F. Shock elicited fighting and Delta-9-tetrahydrocannabinol. Psychopharmacologia, 25:218-228, 1972.

125. Marihuana and Health. A report to Congress from the Secretary, U.S. Department of Health, Education and Welfare, publication #56-310 0, U.S. Government Printing Office, Washington, D.C., 1971.

126. Marihuana and Health. Second Annual Report to Congress from the Secretary, Department of Health, Education and Welfare, publication #75-724 0, U.S. Government Printing Office, Washington, D.C., 1972.

127. Martinez, J.L., Stadnicki, S.W. and Schaeppi, U.H. Delta-9-tetrahydrocannabinol: effects on EEG and behavior of Rhesus monkeys. Life Sciences, 11:643-651, 1972,

128. Masur, J., Martz, R.M.W., Brenieck, D. and Korte, F. Influence of (-)-Delta-9-THC and mescaline on the behavior of rats submitted to food competition situations. Psychopharmacologia, 22:187-194, 1971.

129. Masur, J., Martz, R.M.W.,and Carlini, E.A. Effects of acute and chronic administration of Cannabis sativa and (-)-Delta-9-tetrahydrocannabinol on the behavior of rats in an open-field arena. Psychopharmacologia (Berlin), 19(4):388-397, 1971.

130. Masur, J., Karniol, I.G. and Palermo Neto, J. Cannabis sativa induces "winning" behavior in previously "loser" rats. Journal of Pharmacy and Pharmacology, 24:262, Mar. 1972.

131. Masur, J., Martz, R.M. and Carlini, E.A. The behavior of worker and non-worker rats under the influence of (-)-9-trans-tetrahydrocannabinol, chlorpromazine and amylobaritone. Psychopharmacologia, 25:57-68, 1972.

132. Maynard, D.E., Gurny, O., Pitcher, R.G. and Kierstead, R.W. (-)-Delta-8-tetrahydrocannabinol, two novel in vitro metabolites. Experientia, 27:1154-1155, 1971.

133. McCarthy, T.J. and vanZyl, J.D. Breath analysis of Cannabis smokers. Journal of Pharmacy and Pharmacology, 24:489-490, 1972.

134. McCoy, E.E., Henn, S.W. and Colombini, C.E. The effect of neuro-pharmacological agents on metabolism in vitamin B6 in brain. Advances in Biochemistry and Psychopharmacology, 4(9):93-104, 1972.

135. McDonough, J.H., Manning, F.J. and Elsmore, T.F. Reduction of predatory aggression of rats following administration of Delta-9-tetrahydrocannabinol. Life Science, 2:103-111, 1972.

136. McIsaac, W.M., Fritchie, F.E., Idanpaan-Heikkila, J.E., Ho, B.T. and Englert, L.F. Distribution of marihuana in monkey brain and concomitant behavioral effects. Nature, 230:593-594, April 30, 1971.

137. McMillan, D.E., Dewey, W.L. and Harris, L.S. Characteristics of tetrahydrocannabinol tolerance. Annals of the New York Academy of Sciences, 191:83-99, 1971.

138. Mechoulam, R. Marihuana chemistry. Science, 168:1159-1166, 1970.

139. Mendelson, J.H. et al. In Marihuana: A Signal of Misunderstanding. The technical papers of the first report of the National Commission on Marihuana and Drug Abuse. Appendix I:74-75, 1972.

140. Mikes, R., Hofmann, A. and Waser, P.G. Identification of (-)-Delta-9-6a,10a-trans-tetrahydrocannabinol and two of its metabolites in rats by use of combination gas chromatography-mass spectrometry and mass fragmentography. Biochemical Pharmacology, 20:2469-2476, 1971.

141. Milzoff, J.R., Martz, R. and Harger, R.N. Evaluation of the depressor response of Delta-9-tetrahydrocannabinol in the rat. Federation Proceedings, 31(2):505 Abs., 1972.

142. Miras, C.J. Hashish, its chemistry and pharmacology. G.E.W. Wolstenholme and J. Knight, Eds., pp. 37-52, Little, Brown and Co., Boston, Mass., 1965.

143. Miras, C.J., Kephalas, T.A. and Papadakis, D.P. The effect of hashish extract on the norepinephrine in rabbit brain. Bulletin on Narcotics, 23(1):33-34, 1971.

144. Moreton, J.E. and Davis, W.M. Effects of Delta-9-tetrahydrocannabinol on locomotor activity and on phases of sleep. Pharmacologist, 12(2): 258, 1970.

145. Moreton, J.E. and Davis, W.M. Electroencephalographic study of effects of Delta-9 and Delta-8-tetrahydrocannabinol and Cannabis extract on sleep in the rat. Pharmacologist, 13(2):246, 1971.

146. Moreton, J.E. and Davis, W.M. A simple method for the preparation of injectables of tetrahydrocannabinols and Cannabis extracts. Journal of Pharmacy and Pharmacology, 24:176, 1972.

147. Nahas, G.H. Cannabis sativa. The deceptive weed. New York State Journal of Medicine, 72(7):856-868, April 1972.

148. Nahas, G.H. Toxicology and pharmacology of Cannabis sativa with special reference to Delta-9-THC. Bulletin on Narcotics, 24(2):11-27, 1972.

148a. Nahas, G.H. Marihuana - Deceptive Weed. Raven Press, New York, 1972.

149. Neto, J.P. and Carlini, R.A. Aggressive behavior elicited rats by Cannabis sativa: effects of p-chlorophenylalanine and dopa. European Journal of Pharmacology, 17:215-220, 1972.

150. Newman, L.M., Lutz, M.P., Gould, M.H. and Domino, E.F. Delta-9-tetrahydrocannabinol and ethyl alcohol: evidence for cross-tolerance in the rat. Science, 175:1022-1023, 1972.

151. Nilsson, L.G.J., Nilsson, I.M., Agurell, L., Akermar, B. and Lagerlund, I. Metabolism of Cannabis (hemp) XI. Synthesis of Delta-7-tetrahydrocannabinol and 7-hydroxytetrahydrocannabinol. Acta Chemica Scandinavica, 25:768-769.

152. NSF Japanese/American Joint Conference of Drug Abuse, 1972. (in press)

153. Pace, H.B., Davis, M.W. and Borgen, L.A. Teratogenesis and marihuana. Annals of the New York Academy of Sciences, 191:123-131, 1971.

154. Pars, H.G. and Razdan, R.K. Tetrahydrocannabinols and synthetic analogs. Annals of the New York Academy of Sciences, 191:15-22, 1971.

155. Persaud, I. and Ellington, A. Cannabis in early pregnancy. Lancet, 2(7529):1306, 1967.

156. Persaud, I. and Ellington, A. Teratogenic activity of Cannabis resin. Lancet, 2(7564):406-407, 1968.

157. Peterson, D.W., Cohen, G.M. and Sparber, S.B. The delay of the behavioral effects of Delta-9-tetrahydrocannabinol in rats by 2-diethylaminoethyl 2, 2-diphenylvalerate HCl (SKF 525-A). Life Sciences, 10:1381-1386, 15 Dec. 1971.

158. Phillips, R.N., Brown, D.J. and Forney, R.B. Enhancement of depressant properties of alcohol or barbiturates in combination with aqueous suspended Delta-9-tetrahydrocannabinol in rats. Journal of the Forensic Science Society, 16(2):152-161, 1971.

159. Phillips, R.N., Brown, D.J., Martz, R., Hubbard, J.D. and Forney, R.B. Subacute toxicity of aqueous-suspended Delta-9-tetrahydrocannabinol in rats. Toxicology and Applied Pharmacology, 22:45-49, 1972.

160. Pirch, J.H., Cohn, R.A., Barnes, P.R. and Barratt, E.S. Effects of acute and chronic administration of marihuana extract on the rat electrocorticogram. Neuropharmacology, 11:231-240, 1972.

161. Pitt, C.G., Wildes, J.W., Martin, N.H. and Wall, M.E. Synthesis of (-)-Delta-9(11)-trans-tetrahydrocannabinol. Journal of Organic Chemistry, 36:721-723, 1971.

162. Pradhan, S.N., Bailey, P.T. and Ghosh, P. Effects of Delta-9-tetrahydrocannabinol on a timing behavior in rats. Psychonomic Science, 27:179-181, 1972.

163. Pradhan, S.N., Bailey, P.T. and Ghosh, P. Some behavioral effects of Delta-9-tetrahydrocannabinol in rats. Research Communications in Chemical Pathology and Pharmacology, 3(2):197-204, 1972.

164. Price, P.J., Suk, W.A., Spahn, G.J. and Freeman, A.E. Transformation of Fischer rat embryo cells by the combined action of murine leukemia virus and (-)-trans-Delta-9-tetrahydrocannabinol Proceedings of the Society of Experimental Biology and Medicine, 140(2): 454-456, 1972.

165. Rasmussen, K.E., Rasmussen, S.and Baerheim Svendsen, A. Quantititive determination of cannabinoids in micro-quantities of Cannabis by means of gas liquid chromatography and solid sample injection. United Nations Document ST/SOA/SER.S/35, July 21, 1972.

166. Razdan, R.K., Puttick, A.J., Zitko, B.A. and Handrick, G.R. Hashish VI: stability of (-)-Delta-1 and (-)-Delta-1(6)-tetrahydrocannabinols. Experientia, 28:121-122, 1972.

167. Ribi, R., Smith, R., Strain, M., Petcoff, D. and Filz, C. Purification of Delta-9-tetrahydrocannabinol, an active constituent of marihuana, by accelerate microparticulate gel chromatography. Federation Proceedings, 31:506 Abs. 1972.

168. Robichaud, R.C., Hefner, N.A., Anderson, J.E. and Goldberg, M.E. Effects of Delta-9-tetrahydrocannabinol (THC) on several rodent learning paradigms. Federation Proceedings, 31(2):551 Abs., 1972.

169. Rosenkrantz, H., Thompson, G.R. and Braude, M.C. Oral and parenteral formulations of marihuana constituents. Journal of Pharmaceutical Sciences, 61(7):1106-1112, 1972.

170. Ryrfeldt, A., Ramsay, C.H., Nilsson, I.M., Widman, N. and Agurell, S. Wholebody autoradiography of Delta-1-tetrahydrocannabinol and Delta-1(6)-tetrahydrocannabinol in the mouse. Pharmacokinetic aspects of Delta-1-tetrahydrocannabinol and its metabolites. Acta Pharmaceutica Suecica, (in press).

171. Samrah, H., Lousberg, R.J.J.CH., Bercht, D.A.L., Salemink, C.A., Ham. M. and vanNordwijk, J. On the presence of basic indole components in Cannabis sativa L. United Nations Document, ST/SOA/SER.S/34, May 5, 1972.

172. Santos, M., Sampaio. M.R.P., Fernandes, N.S. and Carlini, E.A. Effects of Cannabis sativa (marihuana) on the fighting behavior of mice. Psychopharmacologia, 8:437-444, 1966.

173. Scheckel, C.L., Boff, E., Dahlen, P.H. and Smart, T. Behavioral effects in monkeys of racemates of two biological active marihuana constituents. Science, 160(3835):1467-1469, 1968.

174. Schildkraut, J.J. and Efron, D.H. The effects of Delta-9-tetranydrocannabinol on the metabolism of norepinephrine in rat brain. Psychopharmacologia, 20:191-196, 1971.

175. Schou, J., Steentoft, Worm, K., Moerkholdt-Andersen, J. and Nielsen, E. Highly sensitive method for gas chromatographic measurement of tetrahydrocannabinol (THC) and cannabinol (CBN). Acta Pharmacologica et Toxicologica, 30:480-482, 1971.

176. Segal, M. and Kenney, A.F. Delta-1(6)-tetrahydrocannabinol: preliminary observations on similarities and differences in central pharmacological effects in the cat. Experientia, 28/7:816-819, 1972.

177. Slatkin, D.J., Doorenbos, N.J., Harris, L.S., Masoud, A.N., Quimby, M.W. and Schiff, P.L. Jr. Chemical constitutent of Cannabis sativa L. root. Journal of Pharmaceutical Sciences, 60:1891-1892, 1971.

178. Sofia, R.D., Ertel, R.J., Dixit, R.N. and Barry, H. III. The effect of 1-tetrahydrocannabinol on the uptake of serotonin by rat brain homogenates. European Journal of Pharmacology, 16:257-259, Oct. 1971.

179. Sofia, R.D. The lethal effects of Delta-1-tetrahydrocannabinol in aggregated and isolated mice following single dose administration. European Journal of Pharmacology, 20:139-142, 1972.

180. Sofia, R.D., Dixit, B.N. and Barry, H. III. The effect of Delta-1 tetrahydrocannabinol on serotonin metabolism in the rat brain. Life Sciences 10(Part I):425-436, 1971.

181. Spaulding, T.C., Dewey, W.L. and Harris, L.S. The pharmacological effects of and the lack of Delta-9-THC blocking activity of phenitrone. Pharmacologist, 13(2):296, 1971.

182. Sperling, F. and Coker, A.A.O. Responses of isolated rat lungs to Delta-9-THC. Federation Proceedings, 31:505, 1972.

183. Sprague, R.A., Rosenkrantz, H., Thompson, G.R. and Braude, M.C. Monkey brain and lung respiration after chronic I.V. treatment with Delta-9-tetrahydrocannabinol. Federation Proceedings, 31:909, 1972.

184. Thompson, G.R., Rosenkrantz, H., Fleischman, R.W. and Braude, M.C. Toxicity of Delta-9-tetrahydrocannabinol (Delta-9-THC) in rhesus monkeys treated per os or intravenous for 28 days. Presented at the Fifth International Meeting of Pharmacology, San Francisco, July 23-28, 1972.

185. Tonge, S.R. and Leonard, B.E. The effect of some hallucinogenic drugs on the amino acid precursors of brain monamines. Life Sciences, 9: 1327-1335, 1970.

186. Truitt, E.B. and Anderson, S.M. Biogenic amines alterations produced in brain by tetrahydrocannabinols and their metabolites. Annals of the New York Academy of Sciences, 191:68-73, 1971.

187. Truitt, E.B., Jr. Biological disposition of tetrahydrocannabinols. Pharmacological Reviews, 23:273-278, 1971.

188. Van Vunakis, H., Farrow, J.T., Gjiken, H.G. and Levine, L. Specificity of the antibody receptor for lysergic acid diethylamide. Proceedings of the National Academy of Sciences U.S.A., 68:1483-1487, 1971.

189. Vree, T.B., Breimer, D.D., Van Ginneken, C.A.M. and VanRossum, J.M. Identification in hashish of tetrahydrocannabinol, cannabidiol and cannabinol analogues with a methyl side-chain. Journal of Pharmacy and Pharmacology, 24:7-12, 1972.

190. Wall, M.E. The in vitro and in vivo metabolism of tetrahydrocannabinol (THC). Annals of the New York Academy of Sciences, 191:23-39, 1971.

191. Wallach, M.B. and Gershon, S. The effects of Delta-8-tetrahydrocannabinol on the electroencephalogram (EEG), reticular formation multiple unit activity (RUA), and sleep of the cat. Federation Proceedings, 31(2): 250, March-April 1972.

192. Waller, C.E. 1972, personal communication.

193. Weinhardt, K.K., Razdan, R.K. and Dalzell, H.C. Hashish synthesis of (-)-7-hydroxy-Delta-1(6)-tetrahydrocannabinol. Tetrahedron Letter, 4827-4830, 1971.

194. Welch, B.L., Welch, A.S., Messiha, F.S. and Berger, H.J. Rapid depletion of adrenal epinephrine and elevation of telencephalic serotonin by (-)-trans-Delta-9-tetrahydrocannabinol in mice. Research Communications in Chemical Pathology and Pharmacology, 2(3): 382-391, 1971.

195. Wursch, M.S., Otis, L.S., Green, D.E.and Forrest, I.S. ^{3}H-Delta-9-tetrahydrocannabinol (THC) metabolism in rhesus and squirrel monkeys. Proceedings of the Western Pharmacological Society, 15:68-73, 1972.

196. Zitko, B.A., Howes, J.F., Razdan, R.K., Dalzell, B.C., Dalzell, H.C., Sheehan, J.C., Pars, H.G., Dewey, W.L. and Harris, L.S. Water-soluble derivatives of Delta-1-tetrahydrocannabinol. Science, 177:442-444, 1972.

EFFECTS IN MAN

Acute Effects

The prominent acute pharmacological effects of marihuana, namely, the characteristic but individually variable subjective "high" and the invariable physiological effects, including an increase in pulse rate and reddening of the eyes, have already been clearly established (56, 44, 33). In the past year the continuing research concentrated on studying the less obvious but potentially important effects of marihuana, of delta-9-THC, and of its metabolites utilizing sophisticated psychological and physiological methodology.

The Question of the Active Ingredient

Since the major psychological and physiological effects of marihuana can be reproduced by the administration of synthetic delta-9-THC, the majority of the studies continued to utilize this compound, and relatively slow progress has been made in exploring the effects of the other, chemically identified ingredients that may play a role either in modifying the effects of delta-9-THC or producing some pharmacological effects of their own.

One of the double-bond isomers of delta-9-THC is delta-8-THC which occurs in relatively small quantities in natural marihuana, and on the basis of animal experiments it has been suspected to possess pharmacological activity comparable to that of delta-9-THC (12, 20).

Orally or intravenously administered delta-8-THC to six human experimental subjects has been shown by Hollister (32, 33) to produce marihuana-like psychological and physiological effects, but it was somewhat less active than delta-9-THC. Its relative potency, both as judged following oral and intravenous administration, is 2:3. In view of this lesser potency, the qualitatively similar clinical effects to delta-9-THC and the relatively low content of this isomer in most cannabis samples, it seems unlikely that varying amounts of this material could account for differences in clinical effects sometimes reported from various cannabis samples.

Two other cannabinoids: cannabinol and cannabichromone, isolated from hashish, were found to be inactive in man. Doses up to 2,000 mcg/kg or 2,500 mcg/kg, respectively, of the two compounds administered orally produced no discernible subjective or physiologic effects (38). Cannabidiol in relatively large smoked doses (25 mg) produced a slight but detectable change in subjective state and increased pulse rate similar to the effects of low doses (2-3 mg) of THC (40).

There have been claims made in a recent paper that the content of delta-9-THC does not explain all biological activity of some Brazilian marihuana samples (42). In this report reference was made to an unpublished clinical study of a Brazilian sample of marihuana which seemed to be about three times more active than would be expected from its delta-9-THC content. Several possible

explanations for this discrepancy were offered, the most likely being that a major portion of the originally present delta-9-THC was converted to cannabinol by the time the chemical analysis was made.

Dose and Route of Administration

While it is generally acknowledged that smoking is the most common way to consume marihuana in this country, researchers who would like to study dose-effect relationships are still troubled by the fact that when marihuana is smoked an uncertain and variable fraction of THC is lost through burning, by being left in the "butt" or "roach", by escaping in the smoke between puffs or by being exhaled following incomplete absorption from the respiratory dead space (44, 83).

Because of these difficulties, many researchers prefer oral or intravenous routes of administration so that at least the delivery of a given dose can be assured. Although 90-95% of the orally administered delta-9-THC and 100 percent (by definition) of the intravenously administered drug is absorbed (50), both of these routes of administration have problems of their own. The speed and degree of absorption of an oral dose of delta-9-THC seems to be greatly influenced by the vehicle used for the preparation (64). Even when the same vehicle was used, absorption of the orally administered drug varied significantly among individuals.

For intravenous administration delta-9-THC is dissolved in absolute ethanol and is injected either through the tubing of a rapidly flowing intravenous infusion of five percent dextrose in water (48, 50, 32) or, after the alcoholic solution is first dispersed in 25 percent human serum albumin and then slowly infused intravenously (65). The first mentioned intravenous technique is preferred when the measurement of dynamic characteristics of distribution and biological half life of a tracer amount of the drug is the primary goal of the investigation (48, 50, 47). The second technique appears to be preferred when larger doses of THC are to be given intravenously or when the effects of a metabolite of THC with unknown potency are to be studied with maximum possible safety (65).

Metabolism of Delta-9-THC

Work continued in the past year to identify the metabolites of delta-9-THC in the plasma, urine and feces of subjects after oral injections or intravenous administration of the radioactive labeled drug and to study the metabolic pattern of delta-9-THC or 11-hydroxy-delta-9-THC.

At least three monohydroxylated metabolites of delta-9-THC have now been positively identified either in human plasma, urine or feces (64, 85). Besides the already known 11-hydroxy-delta-9-THC, 8-A- and 8-B-hydroxy-delta-9-THC have also been identified although they represent a very small portion of the total cannabinoids found in biological specimens at any time after administration of the parent compound (64). 8,11-dihydroxy-delta-9-THC

has also been identified in plasma samples by gas and liquid chromatography-mass spectrometry (86) and appears in plasma in relatively larger amounts than the monohydroxylated metabolites, especially after oral administration of delta-9-THC. Several unidentified metabolites, most likely 11-carboxy acids of various degrees of hydroxylation in free and conjugated form have been found in the urine comprising the majority of the metabolites. These acids are also found to some extent in the feces, but are not found in measurable quantity in the blood.

As far as the relative amounts of the metabolites by the two major routes of excretion are concerned, there seems to be a consensus that the bulk of the metabolites is excreted via the feces, while only about 15-20 percent of the orally, and 20-30 percent of the intravenously administered drug can be found in the urine as metabolites after 72 hours of collection (64, 48). Approximately 20-35 percent of the total dose, however, was still in the various tissues at the time the investigators ceased taking samples.

A curious observation about the metabolic fate of delta-9-THC was made by Perez-Reyes et al. during their studies of blood levels of delta-9-THC after oral administration of the drug (64). At the peak of the psychological "high" the plasma levels of delta-9-THC and 11-hydroxy-delta-9-THC were relatively low, the levels of the dihydroxy metabolite and other, more polar, unidentified metabolites were relatively high. Twelve hours after the injection of delta-9-THC, when the subjects no longer experienced any significant drug effects, the plasma levels of delta-9-THC, surprisingly, increased more than twofold, while the plasma levels of the other metabolites decreased substantially. High levels of delta-9-THC in the plasma without corresponding pharmacological effects suggest that the circulating delta-9-THC is not active, possibly due to strong binding to plasma lipoproteins. The sudden increase several hours after injection is explained by the possibility of mobilization of delta-9-THC from the gall bladder, as bile is secreted following food ingestion and the drug is reabsorbed from the intestines. This view is supported by animal experimental data demonstrating the existence of entero-hepatic circulation for delta-9-THC and its metabolites (13).

The question, whether or not a metabolite is responsible for the psychological activity of delta-9-THC, has been explored in the past year by two groups of investigators (65, 49). Lemberger et al. administered labeled 11-hydroxy-delta-9-THC (1 mg) to three volunteers intravenously using the dextrose infusion technique (49). Psychologic and pharmacologic effects (heart rate, ECG) were continuously evaluated during and after the administration of the drug or the vehicle. Urinary and fecal excretion of total radioactivity and of the unchanged drug were also followed. Characteristic heart rate increase was observed and marihuana-like psychologic symptoms were reported by all three subjects indicating that most of the pharmacologic effects attributable to delta-9-THC or marihuana can be produced by 11-hydroxy-delta-9-THC in man. Perez-Reyes et al. have infused intravenously the same metabolite or delta-9-THC to 12 subjects using the serum albumin technique mentioned earlier (65). The infusion proceeded slowly until the subjects asked for termination of infusion as soon as they felt they had arrived at their derived level of "high" (the subjects were experienced marihuana users, and had also participated in another THC study previously). Heart rate and respiration were

constantly monitored during the experiment. The results indicate that the two compounds are not significantly different in pharmacological activity when injected intravenously in man.

Since 11-hydroxy-delta-9-THC showed a disappearance rate from plasma and excretion rate in the urine and feces similar to those of delta-9-THC, the conclusion was drawn that after the administration of marihuana or hashish, delta-9-THC is first converted to the 11-hydroxy metabolite and that this metabolite is responsible for the majority of the pharmacological effect of marihuana and hashish (49). This conclusion is consistent with the findings of Galanter et al. (23) who found that the time course of blood levels of THC, after smoking it in a spiked placebo, correlated more closely with the time course of the pulse increment than with the time course of the subjective experience. Both pulse increments and THC levels peaked 15 minutes post smoking, while the subjective effects, presumably elicited by the 11-hydroxy metabolite, appeared later, peaked about one hour post smoking and dissipated in the course of about four hours.

Subjective Effects of Marihuana and THC

Conclusive evidence from two controlled studies shows that delta-9-THC is indeed the major psychoactive component of marihuana (23, 19). Galanter et al. (23) administered natural marihuana, synthetic delta-9-THC (both in 10 mg doses) and a placebo cigarette to 12 volunteers on separate days each, a week apart according to a balanced order double blind design. Subjective drug effects were assessed by a 62-item questionnaire essentially developed by Waskow (87). Other physiological and psychomotor tests were also performed. The relative frequency of subjective symptoms in the marihuana and delta-9-THC states indicated a marked similarity in the subjective experiences. In the placebo states the subjective ratings were somewhat similar in constellation, but only about one third as intense as those reported in active drug states. This suggests a strong learned component in the marihuana response. In the other controlled study, Frank et al. (19) compared three active doses of synthetic delta-9-THC with natural marihuana (containing similar doses of delta-9-THC) and placebo in ten normal volunteers giving each dose a week apart in a random order, double blind design. Among the 17 various psychological and physiological measures, the highest dose-response correlations were found in the subjective "high" estimates of the subjects on a 0 to 7 scale. Both studies found natural marihuana somewhat stronger than synthetic delta-9-THC in terms of the intensity of the subjective effects, but the differences were not large enough to suggest any significant role of components other than delta-9-THC in the natural marihuana.

Some controversy still exists as to the role of the pharmacological effects of delta-9-THC (versus the social setting) and learning in the subjective manifestation of the marihuana "high." Indications are that the effect is very much dependent upon the dose of THC consumed.

In relatively high doses, THC invariably produces psychotomimetic or hallucinogenic effects: paresthesias, altered perceptions, difficulty with thinking,

concentrating or speaking, and depersonalization (38, 34). However, in lower, more typical social doses, smoking of marihuana or appropriately prepared THC produces a level of intoxication which is variable, and allows the attitude of the subject, his set and expectations, the setting, and his past experience to interact in a complex way to determine how the subjective state will be labeled and reported (39). Reese Jones maintains that many people have uncritically accepted the belief that marihuana has specific effects on behavior and experience and that these can be readily identified. Such an erroneous model, he continues, has been accepted by both users and professionals and is continually reinforced by the media. Although at high doses such a model may be valid, as the general consensus of experts on the hallucinogenic properties of high doses of THC suggests, at the doses most youthful drug users are discussing there is ample evidence that the effects of marihuana on behavior and subjective experience are often unpredictable from the drug's pharmacologic profile (39).

Other investigators, using moderate doses of smoked or oral marihuana in double blind studies, came to somewhat similar conclusions (11, 67).

Marihuana intoxication, these studies indicate, is not totally a pharmacological state but rather a state very much affected by the subject's expectations and subjective interpretation of drug effects that he is experiencing. The interpretation is based on long-term social learning rather than simply influenced by the social setting. Moreover, the impairment in functions experienced as part of the intoxication can be enhanced or overcome depending on the subjects' motivation (11). The results of these studies also suggest that the frequent marihuana user is better able to control and compensate for the subjective effects as a consequence of a learned response pattern acquired after extended experience with the drug (67).

Physiological Effects

In view of the consistent pharmacological effects of THC and marihuana on pulse rate, further in-depth studies of this cardiovascular response seemed warranted.

Weiss et al. (88) gave delta-9-THC (0.3 mg/kg) orally to eight male volunteers and monitored carefully the various parameters relevant to cardiovascular functions. Recumbent and upright heart rate, recumbent mean arterial blood pressure, forearm blood flow, and calculated forearm conductance all increased significantly following drug administration. Significant shortening of ventricular pre-ejection period and attenuation or abolition of reflex vasoconstriction in response to deep breath were also seen. Mean arterial pressure decreased transiently with head-up tilt and was associated with presyncope in seven subjects although cardio-acceleratory response and forearm arteriolar constriction remained intact. Several of the cardiovascular effects seen appear to be consistent with increased sympathoadrenal activity rather than a direct effect of delta-9-THC on the heart itself. The augmented epinephrine secretion during the six-hour period following delta-9-THC administration, but not during a similar control period, is

consistent with this interpretation. From the data available, however, it cannot be excluded that additional factors, including the subject's psychic responses, may have influenced circulatory functions (88).

The increase in pulse rate and peripheral blood flow induced by cannabis seems to involve beta-adrenergic mechanisms, since pretreatment with propranolol, a beta-adrenergic blocker, prevented these cardiovascular responses to marihuana (88, 2). Marihuana-induced tachycardia, however, cannot be the result from an atropine-like effect on efferent vagal activity since it could still be evoked in a sustained fashion in subjects who were clinically atropinized (2).

These findings have several clinical implications. The age group most frequently involved in traffic accidents is also the one that most commonly smokes marihuana. A persistently high cardiac rate in a patient in an accident, not adequately explained by the clinical situation, might be related to cannabis smoked before the accident. Also, administration of atropine or local anaesthetic containing epinephrine in such patients could enhance and prolong this tachycardia for a dangerously long period (2).

The effect of marihuana on the intraocular pressure, referred to briefly in last year's report on Marihuana and Health, has been further investigated and compared to the effects of synthetic delta-9-THC in a double blind study by researchers at UCLA (19, 18).

Thirty healthy subjects, 21-29 years of age, most of them occasional users of marihuana were selected on the basis of a strict psychological and medical screening process from the large number of students who volunteered for the study. Each subject returned for intoxication and examinations, a total of eight separate occasions, one week apart, receiving natural marihuana and delta-9-THC spiked placebo marihuana in a cigarette of approximately half gram size containing 0, 1, 2 and 4 percent THC in a random order. Evaluation was done on a double blind basis, using applanation tonometry, a precise ophthalmological technique to measure intraocular pressure (18).

The results confirmed the preliminary report, i.e., marihuana decreases intraocular pressure in normal subjects and the effect is dose-related The maximum average decrease observed was about 36 percent after the highest dose of natural marihuana. Furthermore, it was also demonstrated that delta-9-THC, the main psychoactive ingredient of marihuana, is also the main active component in the effect on the intraocular pressure (18).

The obvious practical significance of this effect of THC would be its potential utility as a therapeutic agent in open angle glaucoma, where pathologically increased intraocular pressure due to some impediment of the outflow facility is a cardinal sign. Preliminary evidence from one glaucoma patient suggests that pathologically increased intraocular pressure can indeed be reduced to normal levels for a few hours by the administration of marihuana (31).

The results of this study, however, cannot be generalized to other situations, such as the street use of marihuana. Before natural or synthetic marihuana

can be deemed safe and efficacious for treating this disease, further studies and testing are required.

In view of the frequently reported respiratory difficulties such as bronchitis and asthma in chronic heavy cannabis smokers (54, 82, 30) detailed studies on the acute effects of smoked marihuana and oral delta-9-THC on pulmonary functions have been undertaken (19).

Nineteen healthy, experienced marihuana smokers, who also participated in the intraocular pressure study at UCLA discussed above, were tested by whole body plethysmography before and following acute intoxication with smoked marihuana of similar strength to that used in the intraocular pressure study (80). In 12 subjects the same tests were performed before and after oral administration of placebo, 10 mg, 15 mg and 20 mg delta-9-THC using a random, double blind crossover design. Whole body plethysmography is a relatively sensitive test which is capable of measuring the effect of any irritant on airway resistance within the respiratory passages. The results of this double blind study indicate that both smoked marihuana and oral delta-9-THC cause significant bronchodilation in normal healthy volunteers resulting in a decrease in airway resistance. This bronchodilation appears to be produced by a mechanism other than beta-adrenergic stimulation since the effect could not be blocked by intravenous pre-treatment of propranolol (0.2 mg/kg) (80). This unexpected airway resistance finding needs confirmation by independent investigators and the study will have to be extended to the effects of chronic administration of the drug before its role in pulmonary and respiratory functions can be adequately assessed.

Neurological Effects

It is generally agreed that the acute effects of THC or marihuana is undetectable by simple though expert visual inspection of EEG records (84, 71). Application of sophisticated computerized methodology in combination with EEG, however, can reveal some subtle but potentially important effects, especially after high doses of THC (84, 51, 72). In a scalp EEG record an increase of alpha activity can usually be demonstrated (84, 71) Certain components of both auditory (72) and visual evoked responses (51) from scalp electrodes show amplitude attenuation or peak delay prolongation after high doses of THC. These results are interpreted as THC acting on brain levels higher than the brain stem reticular activating system (51). THC thus seems to act differently from sedatives or alcohol which act primarily at the brain stem level in the central nervous system.

A unique observation on the possible electrophysiological correlates of the marihuana "high" was made by Heath in a patient who, for other medical reasons, had chronically implanted electrodes in various deep structures of his brain (29). The patient, who had a three year history of drug abuse, was asked to smoke a marihuana cigarette on four occasions while his EEG was recorded from the indwelling electrodes. The development of euphoria was associated with the appearance of more distinct high aplitude slow wave activity focally in the septal region. No significant changes in EEG activity

were observed at other deep sites, over the cortex or over the scalp. Nor were similar changes observed in the EEG from deep sites of the brain of the same patient when effects of amphetamine, alcohol and tobacco were studied for comparison with changes induced by marihuana. Since EEG changes in the septal region, in past studies, have been correlated with the pleasure response, it is suggested by Heath that the results in this case probably also reflect functional changes produced by marihuana in the pathways essential to expression of emotion and feeling (29).

Anecdotal reports in the marihuana literature on the occurrence of dreamlike and hallucinatory states resembling dreams, prompted the suggestion that THC might enhance dreaming sleep (34, 36). Since dreaming has been associated with REM (Rapid Eye Movement) sleep, several groups of investigators initiated studies of orally administered THC on all night EEG recordings (19, 68, 21, 1, 41, 37).

Although these studies are still under way, some preliminary data on limited number of subjects have been reported (68, 21, 1, 41). These indicate that, contrary to expectations, on THC nights there was some decrease in time spent in REM sleep with a "REM rebound" to the normal level on the following nights, apparently irrespective of whether THC continued to be given or the drug was withdrawn. The acute effect of THC on the stage 4 type of non-REM sleep was a slight increase in the first night (68, 1) but if THC was given on several consecutive nights, a progressive and apparently significant decrease in this measure was observed (1). Since there seems to be no quick "rebound" of this sleep stage after discontinuation of THC, it may be a sign of long-term effect of chronic administration of THC, but any speculation regarding its significance must await additional confirmation and further studies of this particular phenomenon.

In view of the continuing debate on the relative toxicity of alcohol and marihuana, it was of interest to investigate the effect of marihuana on the vestibular system which plays an important role in maintaining the equilibrium of the body. As it is well known, alcohol and several other drugs can produce serious impairment of this system resulting in ataxia and a loss of equilibrium. In a controlled study, two doses of marihuana (7.5 and 15 mg THC) and a placebo cigarette were given on separate occasions in a random fashion a week apart to 72 volunteers (half of them occasional, half heavy users of marihuana) (78). A sensitive technique, electronystagmography was the main tool of the study but other, clinically routine, vestibular function tests were also performed before and twice after smoking the test cigarette. The results indicate no significant effect on these vestibular function tests by any of the test substances.

In another study seven volunteers were given two doses (0.2 and 0.3 mg/kg) of THC orally on separate occasions and various physiological and neurological tests were performed (37). Typical subjective effects and pulse rate responses were recorded for several hours after ingestion. A modified Romberg test showed no impairment when the test was performed with the eyes open. However, when visual cues were absent (with closed eyes) the ataxia and equilibrium impairment were marked after the higher dose of THC. Other tests, such as

reaction time, visual evoked responses and sleep patterns on continuous EEG showed no drug-related changes (37). Some of the discrepancies between this and the other studies may be related to methodological differences or, especially in the results of the sleep studies, to the small number of subjects which made the results and conclusions relatively uncertain.

Effects on Mental and Motor Performance

There have been several controlled studies performed in the past year to define the areas of mental and motor activities that are affected by marihuana or THC and to establish the role of chronic smoking in the actual performance variables after either smoking (70, 15, 19, 22, 58) or orally ingesting marihuana or THC preparations (66, 19). Carefully controlled conditions were deemed necessary for two major reasons already alluded to: first, because of the confounding effects of set and setting had to be partialled out so as to establish the effects of the drug itself, and second, because the effects of marihuana on many of the performance tests are relatively small and could be clearly demonstrated only in well-controlled situations.

A deficit in short-term memory has again been clearly demonstrated in all of the studies which included an appropriate test of this function in their assessment battery (70, 22, 58, 66).

In several other simple or moderately complex psychomotor tasks the reported findings are still mixed. Reaction time is more frequently reported to be affected by marihuana or THC (32, 66, 51) than not to be affected (22). Tapping speed or Reitan's trail-making is either not affected by the drug (66, 58) or affected only to a moderate degree (66, 15).

Evidence is accumulating more clearly indicating that more complex tasks may be detrimentally affected by marihuana or THC (66, 19, 58). Some of the discrepancies in the reported effects of this drug on psychomotor performances may be related to the findings that occasional and frequent users perform differently under the influence of the drug, with the frequent users showing better performance and a clearer dose response curve than occasional users (66).

Research on the theoretically as well as practically important issues of the possible interaction between THC and other drugs has just begun. It is primarily of theoretical interest, for example, that propranolol, a beta-adrenergic blocking agent, seems to block the cardioaccelerating action (80) or the disruptive effects of the drug on recall and performance tests (15).

It is of more practical interest that THC and alcohol seem to have additive effects on heart rate and conjunctival injection ratings (58), as well as on performance measures of various psychomotor tasks (55, 58, 10). However, alcohol seemed to have no effect on the subjective phenomena produced by THC (except for visual imagery) which were possibly antagonized by the simultaneous ingestion of alcohol (58).

Driver Performance

It is of considerable practical interest whether or not automobile driving performance is adversely affected by marihuana smoking and, if so, how does the impairment produced compare to that produced by alcohol drinking. During the past year several studies have been performed and published both in this country and abroad. One of the studies involved actual driving (right after smoking) over a predetermined driving course. The driving task included both slow forward and backward maneuvering and higher speed (about 25 mph) straight and curved sections, marked out with wooden poles and plastic cones (58). The subject's driving was scored on: hits of cones and poles, rough handling and speed. Supplementary physiological and psychological measures were also obtained during each session. The sessions were designed to give performance data on driving impairment under four experimental conditions, according to a double blind design: placebo smoked; two levels of marihuana (21 and 88 mcg delta-9-THC per kg body weight); and one dose of ethanol (producing an average blood alcohol level of 0.07 percent - the equivalent of about three cocktails). Both the alcohol and the higher dose of cannabis were found to result in poorer car handling performance. Driving speed, on the other hand, was affected only by the higher dose of cannabis, being slightly but consistently slower (about 7 percent). Driving speeds in the alcohol and low cannabis conditions were not significantly different from placebo. In a second driving trial, about three hours after smoking (or drinking) driving speeds as well as car handling performance scores were statistically indistinguishable from each other under all four conditions, suggesting a temporary effect of the drugs lasting for less than three hours (58).

In another study, using a simulated driving test after orally administered doses of delta-9-THC (350, 400 or 450 mcg/kg) and a placebo according to a double blind design, somewhat similar conclusions were reached except that the effect lasted longer (5-6 hours) in these cases (43). THC significantly impaired adaptation to rapidly changing situations in the driving test. At times when rapid decisions and actions were required, prolongation of reaction time, and an increased frequency of wrong and inadequate responses were observed. The degree of impairment seemed to depend on the initial personality structure and/or individual effects of the drug on basic word and attitude.

The aspect of risk taking in driving after marihuana smoking has been studied in a simulated passing task by Dott (14). Twelve marihuana users operated an optical driving simulator under a nonsmoking condition and under three conditions after smoking crude marihuana leaf. The estimated dosages of delta-9-THC in the smoking conditions were 0 mg., 11.25 mg., and 22.5 mg. During each session, each subject was given the opportunity to pass a lead car with the assistance of a passing aid device under conditions of varying risk. During several of these passing trials, there arose an emergency condition that required immediate response in order to avoid an accident. No differences in performance were noted between the nonsmoking and placebo (0 mg. THC) conditions. Subjects under the influence of marihuana completed fewer passes and took more time to make the elective decision as to whether to pass. It would appear that a subject under the influence of marihuana was less likely to accept the increased risk of attempting to complete the passes that were more

hazardous. Marihuana did not affect the number of attempted passes or the number of "accidents" in a significant manner (14).

A comparison with another experiment - in which the same experimental model was used, but with alcohol as the impairing agent - is of considerable interest (52). Enough alcohol was administered to 16 subjects to achieve a mean blood alcohol level of .089 mg percent, and they performed the same simulated passing study. The results indicate that drivers under the influence of alcohol were more aggressive in their behavior and made more errors of judgment than did control subjects. Subjects under the influence of alcohol attempted and completed fewer passes. There were no significant differences noted in the number of attempts or "accidents." Both the alcohol and the marihuana subjects' decision-reaction times were prolonged in elective type passes. Alcohol also affected the lateral position of the vehicle and the tracking range during passes. Marihuana did not (14).

In regard to the mechanisms involved, Dott offers the interpretation that marihuana does appear to reduce vigilance, but the person under its influence is able to compensate effectively in a high stress situation. Alcohol subjects are not able to achieve this compensation. In this respect, it would appear that alcoholic intoxication is more hazardous for traffic safety than is marihuana intoxication (14). In view of the different conclusion drawn by Kielholz (43) from his study of marihuana on the compensation ability of the subjects in a stressful situation, these results should be interpreted with caution pending further investigations.

With the controversial findings in tests using real or simulated driving, it is important that the effects of marihuana on various basic perceptual and motor functions, which are involved in the complex task of driving an automobile, be further elucidated in rigidly controlled experiments.

Moskovitz et al. (59) have reported three sets of experiments designed to compare alcohol and marihuana effects on visual functions. The first set of experiments examined drug influences on the detection of peripheral lights under three levels of central visual information processing demands. The second set studied drug effects on autokinesis (apparent movement of a stationary point source of light) and the third set examined drug effects on visual acuity, dark adaptation and ocular motor control. Each set of experiments used a group of 12 subjects and the drug dosages were either 200 mcg THC per kg of body weight (a relatively high level of social usage) and placebo or three doses of alcohol: zero, 0.414 and 0.828 grams per kg of body weight, each on a separate occasion with a minimum of three days apart. The evaluation of the various visual functions were done on a double blind basis. The results can be summarized as follows:

Marihuana produced a large decrement in peripheral signal detection under three different conditions of central visual information load, including that condition where no central information processing was required. In addition, errors in the central vision task increased under marihuana. Alcohol, on the other hand, did not impair peripheral vision when central vision did not require information processing by the brain. A dose related, significant

impairment of the peripheral vision under both alcohol doses was observed when central information processing was required by the brain (59, 60).

The effect of alcohol is interpreted as a deficit in the ability to divide attention or "time-share," while the effect of marihuana was suggested to be due to momentary lapses of attention - attention in the sense of concentration upon a specific task (59).

The results of the autokinesis studies revealed again a striking difference in the effects between the two drugs. Alcohol produced only an insignificant change in this measure, while marihuana produced a considerable and statistically significant increase in the mean distance of the apparent movement of a stationary light source (74, 59).

Dark adaptation, as measured by the Goldman-Weekers adaptometer was not affected by any of the drug treatment situation (placebo, alcohol or marihuana) (59). This finding is in conflict with earlier, admittedly preliminary findings of difficulties in dark adaptation under marihuana as reported in terms of increased amount of time required to recover from glare (17). Marihuana as well as alcohol produced no effects on visual acuity or on binocular vision and only a small impairment on oculomotor functions (59).

The significance of these studies on visual functions lies in the fact that without understanding the mechanisms inducing the visual deficits in complex perceptual functions found under marihuana, it is difficult to estimate the degree of impairment likely to be found in man-machine interactions such as flying or driving. Only by understanding the mechanisms involved can we attempt to predict marihuana's impact on a host of variables out in the more complex work situation (59).

In an effort to throw some light on the complex interplay between the altered perceptual processes and motor functions, the effects of smoked marihuana and ethanol on human schedule controlled behavior have been compared (10). The behavioral task involved a differential reinforcement of low rate schedule in which subjects were required to space key-press responses at least 20 seconds apart in order to receive a small monetary reinforcement. Another feature of the schedule was that reinforcement was available for a limited period ranging from 0.5 to 4.0 seconds. Subjects received immediate feedback indicating whether a response was premature, correct or late. In a Latin square design, 12 subjects performed the designated task after consuming marihuana cigarettes containing a total of 0, 4, 8 or 16 mg of delta-9-tetrahydrocannabinol, and 12 additional subjects were tested following 0, 0.48, 0.72 or 0.96 g/kg of ethanol. There was a dose-related decrement in reinforced responses after marihuana. Moreover, a reliable shift toward errors of premature responding was observed with increasing doses. Ethanol had no reliable effects on the schedule controlled behavior at any dose. The results indicate that marihuana, in contrast to alcohol, interferes with temporally controlled responding even when there is a maximum of feedback concerning response accuracy. A placebo effect on behavior was found with marihuana but not with ethanol (10).

From these studies it is clear that marihuana at levels of typical social usage does impair visual perceptual performance as well as temporally controlled responses to a significant degree and potential users should be warned that driving under its influence may lead to accidents.

Jamaican Study

Since cannabis use on a large scale is a relatively recent phenomenon in this country, it is difficult to find populations of chronic users who can be studied for possible adverse effects of long-term use. Another difficulty in studying cannabis users in this country is that many of them use other drugs as well, making it difficult to sort out possible adverse effects attributable solely to cannabis. In order to avoid some of these difficulties, the National Institute of Mental Health supported an intensive study of chronic cannabis users in Jamaica (73). This study was undertaken to assess the possible physical and mental effects of cannabis in adult males who had been heavy smokers for many years. Because various portions of this Jamaican study will be referred to in the following sections on the adverse physical and psychological effects of cannabis, we will describe here some relevant aspects of the study design, the sample characteristics, and the level and duration of cannabis usage.

The subjects were from the lower socioeconomic class of Jamaican society and were mainly farmers and fishermen from rural areas, and unskilled laborers from the Kingston area. Sixty subjects, thirty chronic cannabis smokers and thirty matched controls, were hospitalized for six days. During this time detailed medical histories and physical examinations were performed, chest X-rays and electrocardiograms taken, respiratory function tests performed, and a variety of blood chemistry tests were done to assess renal, liver, and hematological function. In addition, thorough psychological and psychiatric assessments were carried out, including psychological testing and EEGs.

The age range of the subjects was from 23 to 53 years, with an average age of 34. Age at first cannabis smoking experience varied from 8 to 36 years. Total years of regular cannabis smoking ranged from 7 to 37 years, with a mean of 17.5 years. The number of marihuana cigarettes smoked per day ranged from 1 to 24, with an average of 7. Potency of cannabis preparations in Jamaica varies but analysis of samples submitted by the subjects revealed a relatively high delta-9-tetrahydrocannabinol content ranging from 0.7 percent to 10.3 percent, with an average of 2.96 percent.

In general, the users and controls seemed well-matched. All but 3 of the cannabis users also smoked tobacco, whereas 8 of the controls did not use tobacco. Alcohol consumption appeared to be roughly the same for both groups.

Chronic Physical Effects

Past reports of the effects of chronic use of cannabis have described a variety of conditions ranging from minor physical effects such as congestion of the ciliary vessels of the eye to organic brain damage. The many problems involved in proving a causal relationship between the chronic use of any drug and a resulting illness have been described in previous reports to Congress (56). Also, the importance of the level of usage of cannabis has been emphasized. In general, there has been little evidence that occasional light use of cannabis has deleterious physical effects. Most reports in the literature of chronic physical effects were of heavy users of cannabis. In this country most usage would be considered light compared to levels common in some Eastern countries where very potent preparations such as hashish are regularly used. Therefore, exposure to toxic substances in cannabis preparations may vary many fold from population to population and chronic physical effects are likely to be dose dependent. Thus, to be meaningful, discussions of toxic physical effects must take into consideration the level of exposure. Almost every drug will have chronic physical effects if given in large enough doses over a sufficient period of time. There is no totally "safe" drug. The safety of a drug only has meaning if discussed in the context of level and characteristics of common usage of the drug.

Recently a new report in this country has described the occurrence of gynecomastia (breast enlargement) in chronic marihuana users (28). Three cases of young males in their twenties with gynecomastia associated with heavy marihuana use for from two to six years were observed. Extensive examinations were performed to rule out other causes such as liver disease or an endocrinological abnormality, however no evidence of other disorders was found. The authors speculate that the chemical similarity between delta-9-tetrahydrocannabinol and the feminizing hormone, estradiol, may have played some role in this phenomenon.

Although some authors have previously reported evidence of liver dysfunction, others have been unable to confirm this finding and in some cases have described liver abnormalities in chronic marihuana users who were later discovered to also be heavy users of alcohol. In the Jamaican study comparisons were made between cannabis users and controls on a number of blood chemistry tests which can indicate liver malfunction. No significant differences were present and no evidence of liver disease was observed in the cannabis users. In Canada, in a preliminary report of a study of 200 regular cannabis users, Oki and Sisson report that there seemed to be no significantly increased incidence of liver disorders in cannabis users as compared to a similar non-cannabis using population (9).

Since the liver seems to be important in the metabolism of the active constituents of cannabis, such as delta-9-tetrahydrocannabinol, there is considerable interest in the possible deleterious effects of cannabis on liver function. Such effects occurring at the levels of chronic usage common in the Western Hemisphere have not been demonstrated.

Respiratory difficulties have in the past been reported in chronic, heavy smokers of cannabis preparations. In last year's Report to Congress it was concluded that there was some evidence to support these observations. In the past year

further case reports and observations have appeared which lend increased credibility to the earlier reports. Henderson et al. report on 200 cases of chronic hashish smokers in the U.S. Army in West Germany who sought treatment for a variety of upper and lower respiratory tract complaints (30). Over 90 percent of these patients additionally smoked cigarettes. Use of hashish was very heavy and ranged up to 600 grams per month. Most of the complaints were relatively minor ones such as sore throat and rhinitis, but 20 of these patients were diagnosed as having bronchitis. In the bronchitis patients chest X-rays were normal except for increased bronchopulmonary markings but pulmonary vital capacity was reported to be 15-40 percent below normal. Six of the bronchitis patients underwent bronchoscopy and biopsy. All of these patients used greater than 50 grams of hashish monthly. Although no gross lesions were seen for biopsy, all samples showed microscopic epithelial alterations such as loss of cilia, hyperplasia, and presence of atypical cells. The authors felt that such abnormal findings were similar to those usually seen in heavy cigarette smokers in an older age group. In a further report from this group, they describe the finding of bronchial biopsies on 17 additional heavy hashish smokers (26). Microscopic abnormalities were observed in every biopsy and included epithelial changes similar to those described above.

In a recent study of the effects of marihuana and tobacco smoke on human lung explants, Leuchtenberger et al. found an increased incidence of cellular abnormalities in both the cultures exposed to marihuana and tobacco as compared to control cultures (89). Initially, the cellular changes were more severe in the tobacco smoke exposed cells than in marihuana smoke exposed cells; however, after this initial period marihuana appeared to produce the same abnormalities as tobacco smoke. However, the marihuana smoke was administered at twice the level of tobacco smoke in this study.

In the Jamaican study, spirometric and arterial blood gas tests of pulmonary function revealed no major statistical differences between cannabis smokers and controls. However, several trends were of interest. There was a tendency for a proportional decrease in the forced expiratory volume, the forced vital capacity, and the peak flow as the number of years and quantity of cannabis and tobacco cigarettes smoked increased. The arterial oxygen of cannabis smokers tended to be lower than that of the controls. However, these trends are difficult to evaluate because a larger proportion of the cannabis smokers also smoked tobacco. In addition, cannabis in Jamaica is often smoked as a mixture with tobacco. For these reasons it was felt that these findings may be more a result of smoking per se than of marihuana smoking as such.

In addition, the Jamaican study showed statistically significant differences in the blood hemoglobins of cannabis users versus controls. Cannabis users had elevated hemoglobin levels and elevated packed red blood cell volumes. Although carboxymethemoglobin levels were not obtained, it was felt that this might be the most reasonable explanation of these findings and the low arterial oxygen. In other words, these findings could be due to an increased production of hemoglobin and red blood cells as a result of a functional hypoxia induced by chronic smoking.

The possibility that chronic cannabis use might cause brain damage is one that has stirred concern and controversy in this country. During the past year

several articles have been published which are relevant to this issue.

Kolansky and Moore have described a series of 13 adults who were regular users of cannabis (three to ten times per week) and who were referred to them for psychiatric evaluation and care because of various psychiatric symptoms (46). These authors feel that their observations reflect a specific pathological organic response in the Central Nervous System to cannabis and speculate widely on the possible biochemical and structural brain lesions that might accompany such a syndrome. They describe a common core of symptomatology which they feel characterizes this syndrome and which includes such things as apathy, mental sluggishness, loss of interest in personal appearances, flattening of affect, sense of well-being, mental confusion, slowed time sense, difficulty with recent memory, and an incapability of completing thoughts during verbal communication. They report that the intensity of symptoms seemed to be related to the level of cannabis use and that in most cases there was either total or partial remission of symptoms after the patient stopped using cannabis. All of these patients were felt to be relatively normal psychologically prior to using cannabis although the authors did not observe this normal baseline but conclude on the basis of clinical history taking that this was the case. The authors strongly feel that the psychological phenomena they observed are causally related to a toxic effect of cannabis on the brain.

Although this report tries to make a causal connection between cannabis and an organic brain syndrome, there are limitations on the conclusions which can validly be drawn by an uncontrolled case report of this sort. While clinical case reports are very useful in medicine in alerting other physicians to possible new syndromes and etiological agents, they cannot provide definitive evidence because of their inherent sampling bias and their lack of control over a multitude of independent variables that may account for the phenomena observed. A number of the symptoms described as part of this cannabis syndrome are not too different from the effects of acute marihuana intoxication. Whether these patients may at times have used cannabis before seeing their psychiatrist or may have been chronically intoxicated is unknown, but some sort of objective knowledge of the drug status of the individual is needed before conclusions about brain cell damage as the cause of these symptoms can be made. Unfortunately, simple body fluid tests for the presence of cannabis products are not yet available to physicians. Hopefully such tests will be available in the future so that the presence or absence of cannabis or other intoxicants such as alcohol and barbiturates can be easily ascertained by the physician who sees such symptomatology. Although these cases were all felt to have had an absence of psychopathology prior to cannabis use, one must wonder why many of them became psychologically dependent on cannabis since only a small fraction of users become chronic users. There is some reason to believe that a high level of pre-existing psychopathology exists in many of those who do become dependent. That these patients got better when they gave up cannabis use is suggestive that cannabis may have been playing some role in their difficulties but other factors may have also played a role. For instance, some of them received psychotherapy and all of them were told that their use of cannabis was causing their difficulty and that they should stop the cannabis use in order to get better. Thus, suggestion on the part of the therapist may have played some role in their improvement. Finally, these authors report no attempt to corroborate their subjective clinical

impressions of brain damage with more objective tests such as EEG's and batteries of neuropsychological tests. While these alternative explanations of their observations may be incorrect, they serve to illustrate the sorts of variables that can complicate any attempt to arrive at definite causal relationships on the basis of clinical case reports.

Tennant and Groesbeck have recently published their observations of the psychiatric complications of 720 hashish smokers in the U.S. Army in West Germany (81). A total of 110 of these patients heavily used hashish, smoking it several times a day to the point that they were chronically intoxicated. The authors were able to prospectively follow 9 of these heavy users for periods of up to two years. These patients eventually discontinued hashish use. In six of these patients, memory, alertness, concentration, and calculating ability appeared to return to normal in two to four weeks after stopping hashish. Three of the nine continued to exhibit intermittent symptoms which were felt to be analogous to those of organic brain damage. With time these episodes became less severe and less frequent. Twenty-three of these 110 patients were first observed during chronic intoxication but later quit the use of hashish. Ten of these 23 continued to exhibit intermittent episodes of memory loss, inability to concentrate, and confusion. These patients denied further use of drugs except alcohol though the authors report no objective corroboration of the patient's drug use such as urine or blood testing during this period.

In a study in Egypt of 850 hashish users compared to 839 nonuser controls, both drawn from a population of prisoners, Souief found differences between users and nonusers on a number of tests which assessed cognitive and psychomotor performance (77). In general the users had poorer scores than the controls. However, these differences may have predated cannabis use or may have been a result of the long-term existence in a particular life style necessitated by participation in the hashish subculture in Egypt.

In the Jamaican study extensive efforts were made to assess the possibility of brain dysfunction in the subjects. EEG's were recorded and every subject received an elaborate battery of neuropsychological tests and a neurological examination. The striking finding in this study was the absence of any significant difference in any of these parameters between the chronic cannabis users and their matched controls. There was no evidence of organic brain damage in any of the subjects in the study, and the psychosocial functioning of the regular cannabis users matched well with the controls and with social expectations for those from that stratum of Jamaican society.

In a study of chronic hashish users in Greece, there were no significant differences between users and a matched control group in the prevalence of EEG abnormalities (16).

In a Canadian study, Campbell studied the EEG's of a group of cannabis users who had become psychotic and compared them with a group of cannabis users who had no psychiatric impairment, and a group of schizophrenic and neurological patients (8). Both the cannabis groups had a high incidence of abnormal EEG's. However, this was a small sample and the cannabis use among these groups was quite variable.

Genetic and Birth Defects

In last year's Report to Congress we indicated that in a small number of preliminary studies on the effect of cannabis on human chromosomes there was little evidence that cannabis caused chromosomal aberations. Also, the number of reports of birth defects in children of mothers who used cannabis was very small. During the past year such reports have continued to be very rare. In a single case report Bogdanoff, et al. reported the birth of an infant with multiple central nervous system abnormalities to a 19 year old mother who had smoked marihuana and had taken multiple drugs including LSD and amphetamines throughout her pregnancy (5). No conclusion can be reached about the role of cannabis, if any, in this case.

There have been further reports of cytogenetic studies on the effects of cannabis on human chromosomes. Stenchever, et al. recently studied the in vitro effect of delta-9-tetrahydrocannabinol on the chromosomes of human lymphocytes (79). In their study, human leucocytes from healthy blood donors were exposed to several concentrations of delta-9-tetrahydrocannabinol in tissue culture. They found no increase in the incidence of chromosome breaks or other defects in any of the cannabis exposed cultures when compared to controls. In the Jamaican study the chromosomes of peripheral blood lymphocytes were examined and comparisons were made between cannabis users and nonusers. No significant differences were found in the incidence of chromosomal abnormality between cannabis users and controls.

At the present time there continues to be little evidence from human case reports and research studies that cannabis preparations have either a significant teratogenic effect or have any significant effect on chromosome breakage. Case reports of children with birth defects born to mothers that used cannabis continue to be very infrequent and almost always are complicated by the use of other drugs. In vitro studies of the effect of delta-9-tetrahydrocannabinol on human chromosomes as well as studies of chromosomes from chronic cannabis users have so far failed to indicate that cannabis causes chromosomal aberations. However, it must be kept in mind that such effects may be dose related. It is possible that very heavy use of cannabis preparations might have a detectable effect. Thus far there have been few reports of cytogenetic studies of very heavily using populations. In addition, the limited findings reported to date need to be confirmed, particularly by other studies of chronic cannabis abusers. In the meantime, caution dictates that care be exercised in the use of cannabis especially during the reproductive years and by young women during pregnancy.

Evidence from recently conducted animal research provides no indication that marihuana, even under conditions of chronic use, is mutagenic or teratogenic. Nevertheless, there is no way to be completely certain that under some condition of use, possibly in interaction with that of other drugs, adverse consequences might not ensue.

Acute Physical Toxicity

As was summarized last year, death from overdose of cannabis is a very rarely reported event. Case reports of death from cannabis overdose continue to be extremely infrequent. This fact, plus evidence from animal toxicity studies indicates that the ratio of lethal dose of cannabis to psychologically effective dose is very large and is much more favorable than that of drugs such as alcohol and many common over-the-counter drugs. This may not be the case for the intravenous injection of a cannabis preparation since a majority of the severe physical reactions to cannabis reported in this country have followed this mode of administration.

Although in the past, isolated reports have associated marihuana with exacerbations of certain chronic illnesses such as epilepsy and diabetes, a causal role has not been established and thus far the deleterious effect of marihuana in these illnesses has not been confirmed. One acute pharmacologic effect of cannabis that has been repeatedly demonstrated in humans is a tachycardia. Some investigators have suggested that the use of cannabis derivatives by people in middle age or people with cardiac illnesses might present some hazard (61). Others have suggested the possibility that there might be a deleterious interaction between cannabis derivatives and various vasoactive compounds used in medical practice (2). So far there have been few case reports in this country which would confirm these concerns.

Cannabis and Psychopathology

Previous reports to Congress have pointed out that marihuana use may be associated with certain less severe psychological reactions such as depressive and panic reactions, particularly in inexperienced users. Also, there seemed to be some evidence that the sudden exposure of an individual to greater amounts of cannabis than that to which he was tolerant might cause a toxic psychosis. These psychoses appeared to be relatively infrequent and self-limited, usually resolving in a few days to a few weeks when exposure to cannabis was terminated. Although cannabis has been claimed to be a cause of chronic psychoses and an amotivational syndrome, there appeared to be little well-controlled evidence to support this though systematic investigation in this area was rare.

In the past year a number of case reports have appeared which have described psychiatric problems in association with cannabis use. Tennant and Groesbeck have reported on the psychiatric phenomena associated with hashish use among U.S. Army personnel in West Germany (81). They received 720 referrals of hashish smokers from a population of 36,000 soldiers. Of these patients, 392 were occasional users and limited their use to 10 to 12 grams monthly. In these light users there were no indications of adverse psychological or behavioral effects and their major complaints centered around minor respiratory problems such as sore throats. Eighteen patients were seen because of a panic reaction or toxic psychosis after a single high dose of hashish. Psychotic manifestations in these patients dissipated within three days following treatment with phenothiazines. Eighty-five other patients were referred for

treatment of an acute toxic type psychosis after use of hashish and other drugs in combination. These other drugs included alcohol, various hallucinogens, amphetamines, and sedatives. In 115 patients a psychosis similar to schizophrenia occurred and progressed to a chronic psychotic phase similar to chronic schizophrenia. Almost all of these patients were very heavy hashish users (several times daily). Finally, 110 of these patients were very heavy users of hashish who were referred for evaluation because of being in a chronically intoxicated state which seriously interfered with their psychosocial functioning. These subjects appeared to be analogous to chronic alcoholics. It must be emphasized that these levels of usage are extremely high compared to common American usage, and the authors estimate that they may be equivalent to as much as 500 to 6,000 marihuana cigarettes per month of the street variety found in the United States. The authors conclude that 10 to 12 grams or less per month of hashish was without apparent adverse mental effects while heavier levels of usage and simultaneous use of other psychoactive drugs may produce a variety of adverse mental effects ranging from toxic psychoses to a chronically intoxicated state.

In Scandinavia, Bernhardson and Gunne investigated the number of cases of psychosis seen in association with cannabis use (4). They mailed questionnaires to psychiatric clinics and mental hospitals throughout Sweden and found 66 cases of psychosis in cannabis users. Of these, 20 were excluded because of the predominant use of other drugs and little use of cannabis. Of the remaining 46 cases of psychosis, 24 were of an acute nature (1 to 5 weeks) and 22 were chronic (greater than 4 months and continuing at the time of the study). Hashish was the preparation of cannabis most commonly used and use was quite high by American standards (2 to 15 grams daily). A majority of the chronic psychoses occurred in individuals who had a history of psychosis prior to cannabis use and almost all of these cases appeared to be chronic schizophrenia. Only two of the 24 patients who had an acute psychosis, however, had had a previous history of a psychotic episode. In many of those who had an acute psychotic episode there had been a considerable increase in cannabis use just prior to the psychosis.

Geerlings et al. report a survey of acute adverse drug reactions seen in the emergency room of the major hospital in Amsterdam (24). Adverse reactions to alcohol were the most frequent problem with reactions to psychotomimetics, stimulants and cannabis following in that order. In general, the reactions to cannabis were not severe and consisted mostly of panic reactions though 3 cases were seen in which hallucinations or paranoid ideation was present.

In a recent report, Heath has described the occurrence of high amplitude, slow-wave EEG activity recorded from an electrode implanted in the septal area of the brain (29). These recordings were made while the subject smoked marihuana and described his subjective state as one of euphoria. The same author has previously reported recording abnormal EEG activity in the human septal area in psychotic patients. The implications of this finding are as yet unclear.

Since case reports rarely make it possible to determine a causal association between cannabis and a particular psychiatric syndrome, those studies which have examined the relationship of cannabis use to the level of psychological health of the user are of interest.

Linn sent questionnaires to 1000 randomly picked university students (53). These questionnaires gathered information on the individual's drug history and also included a psychiatric symptom checklist. On the basis of drug history the students fell into four categories; those currently using marihuana, those who had used in the past but were not now using, those who were nonusers but who had had the opportunity to try marihuana, and those who were nonusers and had never had an opportunity to try marihuana. Cannabis use correlated well with high scores on the psychiatric symptomatology checklist. Also nonusers who had never had an opportunity to try marihuana but who indicated they would like to use it had higher scores on the symptom checklist than those who said they would not use marihuana even if it were available to them. Although this seems to suggest that the presence of psychiatric symptoms may predispose to marihuana use there was some support in the study for a different interpretation. For example, students who had the strongest introspective-psychological identification (e.g., "psychological mindedness") were those most likely to be users and nonusers with no opportunity to try marihuana who had high scores in "psychological mindedness" were also those most likely to be willing to use marihuana if it was available. This suggests that marihuana users may be people who are more likely to describe themselves using psychological concepts and thus the high symptomatology scores may not reflect real psychopathology.

Harmatz et al. in a study of young adult applicants to a drug research program found that more users than nonusers were found among those who showed psychiatric impairment (27). Shearn and Fitzgibbons compared the frequency of drug use (including marihuana) of 167 young psychiatric in-patients with the frequency of drug use in college students (75). There was a much higher frequency in the psychiatric patients. Burke and Eichberg in a study of the personality characteristics of adolescent users of non-narcotic drugs of abuse found a broad spectrum of psychopathology (7).

Klapper et al. studied the cognitive performance of subjects who had experimentally received a synthetic derivative of delta-9-tetrahydrocannabinol (45). They selected a group of drug sensitive subjects and a group of drug resistant subjects based on their cognitive performance after receiving the drug. They found significant personality differences as measured by the Minnesota Multiphasic Personality Inventory, between drug sensitive and resistant subjects. This study seems to confirm and correlate well with previous studies which have indicated the importance of psychological set in the effects of cannabis.

One possible adverse psychological effect of cannabis that has received widespread attention is the so-called amotivational syndrome. Clinical case reports continue to appear from time to time describing an association between cannabis and a deviation from conventional motivation (3). For instance, the 13 cases described by Kolansky and Moore seem to have as one of their common features (in addition to the previously discussed organic symptoms) a decrease in conventional motivation. Several of these patients seemed to lose interest in their profession or occupation, acquire new, less competitive values, and become interested in various political, philosophical, or religious systems. The interpretation of this sort of change is very difficult since illicit drug use in the United States is often closely associated with a counterculture movement that emphasizes just such values as these as being preferable to

conventional ideas. It is practically impossible to tell from anecdotal case reports whether cannabis caused the change in behavior and values or whether the change in values and behavior caused the individual to become involved in cannabis use. So far, well controlled studies to examine this problem are virtually non-existent. The results of the Jamaican study indicate that such an amotivational syndrome is not associated with regular cannabis use in that society. These results suggest that factors other than cannabis may be important in causing the changes described in this country.

A further problem in defining an amotivational syndrome is in delineating it from states caused by intoxication with the drug. It is quite possible that cannabis may decrease motivation if the individual is chronically or even frequently intoxicated by it. Some experimental evidence to support this comes from a study conducted by the Addiction Research Foundation of the behavioral consequences of administration of marihuana in a controlled setting (9). They found that when subjects were forced to consume larger daily quantities of cannabis than they wished, there was a decrease in work productivity. Mendelson and Meyer, however, in their study of experimental administration of marihuana did not find any consistent alteration in pattern of work over a 21 day period (57). However, most authors who describe the amotivational syndrome do not seem to be talking about a direct result of frequent intoxication but rather emphasize some lasting change in behavior and personality presumably due to permanent or semi-permanent organic brain changes. For this reason, the fate of the entity, amotivational syndrome, will probably ultimately depend on the demonstration or lack of demonstration of specific organic brain lesions which can be causally related to cannabis. The continued use of uncontrolled anecdotal reports to support the existence of this syndrome will probably add little to clarifying the situation.

In summary, the acute psychoses reported by Tennant and Bernhardson after sudden increase in cannabis use or a single high dose seem to be compatible with previous reports of a cannabis toxic psychosis which is usually short-lived, self-limited, and without apparent lasting psychological consequences. Tennant's and Geerling's reports suggest that such acute psychoses due to cannabis alone are not frequent occurrences. The acute psychoses occurring after use of hashish in combination with other drugs emphasize the possibility of synergistic interactions of various drugs of abuse. The chronic psychoses which occurred in association with cannabis use seem, for the most part, to be little different from chronic schizophrenia. In Bernhardson's study, a majority of those with chronic psychosis had a psychosis prior to cannabis use, thus making it doubtful that cannabis was a cause. Most of those chronic patients in both Tennant's and Bernhardson's reports who did not have prior psychoses come from the age group that is at highest risk for the onset of schizophrenia; therefore, some sort of appropriate control population would have to be examined before an association between cannabis and chronic psychosis could be established. Even this would not establish a causal relationship. Therefore, cannabis as a sufficient cause of chronic psychosis seems to remain unproven. This, of course, does not rule out the possibility that heavy cannabis use may play a role in precipitating or aggravating chronic schizophrenic psychoses.

A number of studies have suggested that cannabis use in this country, particularly heavy use and use in conjunction with other drugs, is associated with considerable psychopathology and that this psychopathology may predate the drug use. Further studies are needed to clarify this issue. The existence of an amotivational syndrome continues to be reported. In the absence of evidence from controlled studies (such as the Jamaican study) that such a syndrome is causally related to cannabis, it remains a condition whose existence and characteristics will probably be in doubt unless an association between it and organic brain changes due to cannabis can be unequivocally demonstrated.

References

1. Barratt, E., Beaver, W., White, R., Blakeny, D. and Adams, P., The effects of chronic use of marihuana on sleep and perceptual-motor performance in humans, paper presented at symposium on aeromedical aspects of marihuana, Oklahoma City, June 14, 1972.

2. Beaconsfield, P., Ginsburg, J., Rainsbury, R., Marihuana smoking, cardiovascular effects in man and possible mechanisms, New England Journal of Medicine, 287:209-12, 3 August, 1972.

3. Berman, S., Marihuana: A study of toxic drug reaction among adolescents, Medical Annals, District of Columbia, 40:742-4, December, 1971.

4. Bernhardson, G., Gunne, L.M., Forty-six cases of psychosis in cannabis abusers, International Journal of Addiction, 7:9-16, 1972.

5. Bogdanoff, B., Rorke, L.B., Yanoff, M., Warren, W.S., Brain and eye abnormalities, possible sequelae to prenatal use of multiple drugs including LSD, American Journal of Diseases of Children, 123:145-8, February, 1972.

6. Bright, T.D., Kiplinger, G.F., Brown, D., Phillips, J. and Forney, R.B., Effects of beta-adrenergic blockade on marihuana-induced tachycardia, report of the 33rd Annual Scientific Meeting, Committee on Problems of Drug Dependence, National Academy of Sciences, Toronto, 16-17 February, 1971, Volume II, 1737-1744.

7. Burke, E.L., Eichberg, R.H., Personality characteristics of adolescent users of dangerous drugs as indicated by the Minnesota Multiphasic Personality Inventory, Journal of Nervous and Mental Diseases, 154: 291-301, April, 1972.

8. Campbell, D.R., The electroencephalogram in cannabis associated psychosis, Canadian Psychiatric Association Journal, 16:161-165, 1971.

9. Cannabis: A report of the commission of inquiry into the non-medical use of drugs, 145-152, Information Canada, Ottawa, 1972.

10. Cappell, H., Webster, C.D., Herring, B.S., Ginsberg, R., Alcohol and marihuana: A comparison of effects on a temporally controlled operant in humans, Journal of Pharmacology and Experimental Therapeutics, 182:195-203, August, 1972.

11. Carlin, A.S., The role of side effects and central effects in the social facilitation of marihuana intoxication, paper presented at the 80th Annual Meeting of the American Psychology Association in Honolulu, Hawaii, September 1-8, 1972.

12. Christensen, C.W., Fredenthal, R.I., Gidley, J.T., Rosenfeld, R., Boegli, G., Testino, L., Brine, D.R., Pitt, C.G., and Wall, M.E., Activity of Delta-8- and Delta-9-tetrahydrocannabinol and related compounds in the mouse, Science, 172:165-167, 1971.

13. Dewey, W.L., and Turk, R.F., The excretion and metabolism of 3H-Delta-9-THC in intact and bile-duct cannulated rats, Federal Proceedings, 31:506, abstract, 1972.

14. Dott, A.B., Effect of marihuana on risk acceptance in a simulated passing task, PHS publication, U.S. Government Printing Office, Washington, D.C., 1972.

15. Drew, W.G., Kiplinger, G.F., Miller, L.L., Marx, M., Effects of propranolol on marihuana-induced cognitive dysfunctioning, Clinical Pharmacology and Therapeutics, 13:526-33, July-August, 1972.

16. Fink, M., International Association for Psychiatric Research, Inc., USPHS, contract No. HSM-42-70-98.

17. Frank, I.M., Hepler, R.S., Stier, S., and Rickles, W., Marihuana tobacco and functions affecting driving, (paper presented at American Psychiatric Association, Annual Meeting, Washington, D.C., May, 1971.)

18. Frank, I.M., Hepler, R.S., Epps, L., Ungerleider, J.T., and Szara, S., Marihuana and Delta-9-THC: effects on intraocular pressure in young adults, Fifth International Congress on Pharmacology, San Francisco, July 26, 1972, page 71 abstract of volunteer papers.

19. Frank, I., (principal investigator), UCLA, NIMH contract HSM-42-71-89.

20. Frankenheim, J.M., McMillan, D.E. and Harris, L.S., Effects of 1-Delta-9- and 1-Delta-8-trans-tetrahydrocannabinol and cannabinol on schedule-controlled behavior of pigeons and rats, Journal of Pharmacology and Experimental Therapeutics, 178:241-251, 1971.

21. Freemon, F.R., Effects of marihuana on sleeping states, Journal of American Medical Association, 220:1364-5, 5 June, 1972.

22. Galanter, M., Weingartner, H., Vaughan, T.B., Roth, W.T., and Wyatt, R.J., Delta-9-transtetra-hydrocannabinol and natural marihuana: A controlled comparison, Archives of General Psychiatry, in press.

23. Galanter, M., Wyatt, R.J., Lemberger, L., Weingartner, H., Vaughan, T.B., Roth, W.T. Effects on humans of Delta-9-tetrahydrocannabinol administered by smoking. Science, 176:934-6, 26 May 1972.

24. Geerlings, P.J., Silbermann, R.M., Schalken, H.F., Acute adverse reactions to drug-taking, Acta Psychiatrica Scandinavica, 48:22-9, 1972.

25. Grant, I., Rochford, J., Fleming, T., and Stunkard, A., A neuropsychologic assessment of the effects of moderate marihuana use, (accepted for publication), Journal of Nervous and Mental Disease.

26. Guerry, R.L., Henderson, R.L., Tennant, F.S., and Johnston, W.W., Histopathologic changes in hashish smokers.

27. Harmatz, J.S., Shader, R.I., Salzman, C., Marihuana users and non-users, personality test differences, Archives of General Psychiatry, 26:108-12, February, 1972.

28. Harmon, J. and Abapoulios, M.A., Gynecomastia in marihuana users, The New England Journal of Medicine, 287:936, 2 November, 1972.

29. Heath, R.G., Marihuana, effects on deep and surface electroencephalograms of man, Archives of General Psychiatry, 26:577-84, June, 1972.

30. Henderson, R.L., Tennant, F.S., Guerry, R., Respiratory manifestations of hashish smoking, Archives of Otolaryngology, 95:248-51, March, 1972.

31. Hepler, R.S., Frank, I.M., and Ungerleider, J.T., Marihuana smoking and intraocular pressure in young adults, paper presented at the Annual Meeting of the Association for Research in Ophthalmology and Vision, Sarasota, Florida, April 26, 1972.

32. Hollister, L., and Gillespie, H.K., Delta-8- and Delta-9-THC; comparison in man by oral and intravenous administration, paper submitted for publication in Clinical Pharmacology and Therapeutics.

33. Hollister, L.E., Actions of various marihuana derivatives in man, Pharmacological Reviews, 23:349-57, December, 1971.

34. Hollister, L., Status report on clinical pharmacology of marihuana, Annals of the New York Academy of Sciences, 191:132-141 (1971).

35. Hollister, L.E. and Tinklenberg, J.R., Subchronic oral doses of marihuana extract, submitted for publication.

36. Hollister, L.E., Marihuana in man - three years later, Science, 172:21-29.

37. Hosko, M.J. and Wang, R.I.H., Effects of orally administered Delta-9-tetrahydrocannabinol in human volunteers, submitted for publication (to Clinical Pharmacology and Therapeutics.)

38. Jasinski, D.R., Haertzen, C.A. and Isbell, H., Review of the effects in man of marihuana and THC's on subjective state and physiological functioning. Annals of the New York Academy of Sciences. 191:196-205, 1971.

39. Jones, R.T., Marihuana-induced "High": Influence of expectation, setting & previous drug experience, Pharmacological Reviews, 23:359-69, December, 1971.

40. Jones, R.T., Unpublished observation, progress report, grant MH15842-05.

41. Kaler, A., Hanley, J., Rickles, W., Kanas, N., Baker, M., and Goring, P., Effects of marihuana administration and withdrawal in chronic and noise subjects, Psychophysiology, 9:92 (1972).

42. Karuiol, I.G. and Copliw, E.A., The Content of (-) delta-9-Trans-THC does not explain all biological activity of some brasilian marihuana samples, Journal of Pharmacy and Pharmacology, 24:833-5, 1972 (October).

43. Kielholz, P., Goldberg, L., Hobi, V., Ladewig, D., Reggiani, G. and Richter, R., (Hashish and driving behavior, an experimental study) Deutsche Medizinische Wochenschrift, 97:789-94, 19 May 1972.

44. Kiplinger, G.F., Manno, J.E., Dose-response relationships to cannabis in human subjects, Pharmacological Reviews, 23:339-47, December, 1971.

45. Klapper, J.A., McColloch, M.A., Sidell, F.R., The effect on personality of reactivity to 1, 2-dimethyl-heptyl THC, Archives of General Psychiatry, 26:483-5, May, 1972.

46. Kolansky, H. and Moore, W.T., Toxic effects of chronic marihuana use, Journal of American Medical Association, 222:35-37, 2 October, 1972.

47. Lemberger, L., Axelrod, J. and Kopin, I.J., Metabolism and disposition of delta-9-THC in man, Pharmacological Reviews, 23:371-80, December, 1971.

48. Lemberger, L., Axelrod, J. and Kopin, I., Metabolism and disposition of THC's in naive subjects and chronic marihuana users, Annals of the New York Academy of Sciences, 191:142-154, 1971.

49. Lemberger, L., Crabtree, R.E., and Rowe, H.M., 11-hydroxy-delta-9-tetrahydrocannabinol: pharmacology disposition, and metabolism of a major metabolite of marihuana in man, Science, 177:62-64, July 7, 1972.

50. Lemberger, L., Weiss, J.L., Watanabe, A.M., Galanter, I.M., Wyatt, R.J. and Cardon, P.V., Delta-9-tetrahydrocannabinol, temporal correlation of the psychological effects and blood levels after various routes of administration, New England Journal of Medicine, 286:685-688, 1972.

51. Lewis, E.G., Dustman, R.E., Peters, B.A. and Beck, E., Influence of Delta-9-THC on the human visual evoked response. Proceedings of the 80th Annual Convention, American Psychiatric Association, 1972, 811-812.

52. Light, W.O. and Keiper, C.A., Effects of moderate blood alcohol labels on automotive passing behavior, ICRL-RR-69-4, Providence, Rhode Island, Injury Control Research Laboratory, (1969).

53. Linn, L.S., Psychopathology and experience with marihuana, British Journal of Addiction, 67:55-64, March, 1972.

54. Mann, P.E.G., Finley, T.N., and Ladman, A.J., Marihuana smoking - a study of its effects on alveolar lining material and pulmonary macrophages recovered by bronchopulmonary lavage, Journal of Clinical Investigation, 49(6):60a-61a, June, 1970.

55. Manno, J.E., Kiplinger, G.F., Scholz, N., The influence of alcohol and marihuana on motor and mental performance, Clinical Pharmacology and Therapeutics, 12:202-11, March-April, 1971.

56. Marihuana and Health, Second Annual Report to Congress from the Secretary, Department of Health, Education and Welfare, publication #75-724 0, U.S. Government Printing Office, Washington, D.C., 1972.

57. Marihuana: A signal of misunderstanding, appendix, Volume I: 38-43, U.S. Government Printing Office, Washington, D.C., 1972.

58. Miller, R.D., Hansteen, R.W., Lehmann, H.E., Reid, L., Lonero, L., Adamec, C., Theodore, L., and Jones, B., The commission's experimental studies of acute effects of marihuana, Delta-9-THC and alcohol in humans, paper presented at the meeting of the International College of Neuro-Psychopharmacology in Copenhagen on August 13-17, 1972.

59. Moskowitz, H., A comparison of the effects of marihuana and alcohol on visual function, 129-150, in: Lewis, M.F. (Editor), Current Research in Marihuana, Academic Press, 1972.

60. Moskowitz, H., Sharma, S. and McGlothlin, W., Effect of marihuana upon peripheral vision as a function of the information processing demands in central vision, Perceptual and Motor Skills, 1972, 35:875-882.

61. Nahas, G.G., Cannabis sativa: the deceptive weed, New York State Journal of Medicine, 72:856-68, 1 April, 1972.

62. Nahas, G.G., Effects of hashish consumption in Egypt, New England Journal of Medicine, 287:310, 10 August, 1972.

63. Nahas, G.G., Toxicology and pharmacology of Cannabis Sativa with special reference to Delta-9-THC, Bulletin on Narcotics, 24:11-27, April-June, 1972.

64. Perez-Reyes, M., Lipton, M.A., Timmons, M.C., Wall, M.E., Brine, D.R., and Davis, K.H., The clinical pharmacology of orally administered Delta-9-THC, Clinical Pharmacology and Therapeutics, in press.

65. Perez-Reyes, M., Timmons, M.C., Lipton, M.A., Davis, K.H. and Wall, M.E., Intravenous injection in man of Delta-9-tetrahydrocannabinol and 11-hydroxy-delta-9-tetrahydrocannabinol, Science, 171:633-635, August 18, 1972.

66. Peters, B.A., Lewis, E.G., Dustman, R.E., and Beck, E.C., Sensory, perceptual motor and cognitive functioning following oral administration of varying doses of Delta-9-THC, submitted for publication.

67. Peters, B.A., Lewis, E.G., Dustman, R.E., and Beck, E.C., Subjective reports following oral administration of varying doses of Delta-9-THC, submitted for publication.

68. Pivik, R.T., Zarcone, V., Dement, W.C., Hollister, L.E., Delta-9-THC and synhexl: effects on human sleep patterns, Clinical Pharmacology and Therapeutics, 13:426-35, May-June, 1972.

69. Pivik, T., Zarcone, V., Hollister, L.E. and Dement, W., Effects of hallucinogenic agents on sleep, Psychopharmacology, 6:261 (1969).

70. Rickles, W.H., Cohen, M.J., Whitaker, C.A. and McIntyre, K.E., Marihuana induced state-dependent verbal learning in humans, submitted for publication.

71. Rodin, E.A., Domino, E.F., Effects of acute marihuana smoking on the EEG, Electroencephalographic Clinical Neurophysiology, 29:321, September, 1970.

72. Roth, W.T., Galanter, M., Weingartner, H., Vaughan, T.B., and Wyatt, R.J., The effect of marihuana and synthetic Delta-9-THC on the auditory evoked response and background EEG in humans, unpublished manuscript.

73. Rubin, V., Research institute for the study of man, United States Public Health Service Contract #HSM 42-70-97.

74. Sharma, S. and Moskowitz, H., Effect of marihuana on the visual autokinetic phenomenon, Perceptual and Motor Skills, 35:891-4, (1972).

75. Shearn, C.R., Fitzgibbons, D.J., Patterns of drug use in a population of youthful psychiatric patients, American Journal of Psychiatry, 128:1381-7, May, 1972.

76. Siegel, R.K., and Jarvik, M.E., unpublished observation.

77. Souief, M.I., in The Use Of Cannabis: report of a World Health Organization Group, Bulletin on Narcotics, 24:11-19, January-March, 1972.

78. Spector, M., Acute vestibular effects of marihuana, submitted for publication.

79. Stenchever M.A. and Allen, M., The effect of Delta-9-tetrahydrocannabinol on the chromosomes of human lymphocytes In Vitro, (accepted for publication) American Journal of Obstetrics and Gynecology, 1972.

80. Tashkin, D.P., Shapiro, B.J. and Frank, I.M. Specific airway conductance (SGA) following smoked marihuana (MG) and oral Delta-9-THC in healthy young males, paper presented at the meeting of the American Federation for Clinical Research, 1973.

81. Tennant, F.S., Jr., Groesbeck, D.J. Psychiatric effects of hashish, Archives of General Psychiatry, 27:133-6, July 1972.

82. Tennant, F.S., Preble, M., Prendergast, T.J. and Ventry, P. Medical manifestations associated with hashish, Journal of the American Medical Association, 216:1965-1969, 21 June 1971.

83. Truitt, E.B., Jr. Biologic disposition of THC, Pharmacological Reviews, 23:273-278.

84. Volavka, J., Dornbush, R., Feldstein, S., Clare, G., Zaks, A., Fink, M. and Freedman, M. Marihuana, EEG, and behavior, Annals of the New York Academy of Science, 191:206-215 (1971).

85. Wall, M.E. The in vitro and in vivo metabolism of tetrahydrocannabinol (THC), Annals of the New York Academy of Science, 191:23-39, 1971.

86. Wall, M.E., unpublished observation, Annual Progress Report, HSM 42-71-95, (1972).

87. Waskow, I.E., Olsson, J.E., Salzman, C., and Katz, M.M. Psychological effects of THC, Archives of General Psychiatry, 22(2):97-107, 1970.

88. Weiss, J.L., Watanabe, A.M., Lemberger, L., Taurarkin, N.R. and Cardon, P.V. Cardiovascular effects of Delta-9-THC in man, Clinical Pharmacology and Therapeutics, 13:671-684, 1972 (September-October).

89. Leuchtenberger, C., Leuchtenberger, R. and Schneider, A. Effects of marijuana and tobacco smoke on human lung physiology, Nature, 241:137-139, January 12, 1973.

FUTURE RESEARCH DIRECTIONS

As this and the earlier editions of the Marihuana and Health Report readily attest, we have had an exponential increase in our knowledge of marihuana in recent years. Characteristically, as our knowledge has increased so has awareness of our ignorance in many areas and of the need for additional data. The purpose of this section is to briefly outline some of the important research issues that require study in the future. For convenience we will discuss these needs from a psychosocial and biomedical standpoint.

There is a need for more focused studies on the epidemiology of marihuana use and especially on the family, institutional and peer influences on use patterns. One difficulty with much of the work that has been done in the past is that it has examined drug use at a particular point but not over a period of time. Longitudinal studies over a period of several years or more can contribute much to our presently limited understanding of the implications of cannabis use. It would be very useful to know, for example, what happens with respect to drug use and other aspects of life style as the youthful user passes through the educational process and becomes involved with the demands of adult life and a career.

Longitudinal studies would go a long way toward clarifying the extent to which drug use and changes in conventional motivation that have been alleged to result from it are related. Almost certainly the number of users who "drop out" of more conventional society is small and what evidence exists suggests a preexisting disenchantment with more conventional values. Even among this group, however, little is known about life histories and the degree to which there is a return to more conventional pursuits following a period of estrangement.

One of the problems that has made data from various parts of the country and from different studies difficult to compare has been a lack of consistency in methods of data collection and interpretation of results. While few, if any, studies now limit themselves to examining whether the respondents have simply "ever used" marihuana, it is important that current patterns of use be examined in a way that permits more sophisticated analysis of use patterns along many dimensions. Efforts are currently underway to encourage more thoughtful data collection and more sophisticated epidemiological approaches to examining drug use patterns.

While our understanding of the nature and extent of marihuana use has increased tremendously in the past several years, there are still a number of specific areas in which increased knowledge is greatly needed. Relatively little is known about the extent of on-the-job use of marihuana in industry although there have been reports that such use is occurring with greater frequency.

A systematic knowledge and understanding of marihuana use in various minority groups would be valuable and might also enhance our understanding of the ways in which different groups informally cope with the issue. It is well known that attitudes toward the use of alcohol, for example, vary greatly among different ethnic groups and that these attitudes play a role in the level of abuse

that occurs. A better understanding of the genesis of attitudes toward use and the user in different groups may help us to discourage drug abuse whether of marihuana or of other drugs.

Although the difficulties of setting up well controlled studies of cannabis use overseas remain formidable, there is a continuing need to do so. It will be many years before the number of long term domestic users has increased to the point where large scale assessment of chronic risk is possible. In order to detect possible infrequent hazards it is necessary that we study larger populations than has been done in the past. Such studies, incorporating both biomedical and social science research techniques, can also give us significant insights into the types of drug user, the methods of induction into different use patterns, factors governing persistent use and those psychosocial factors that encourage or discourage excessive cannabis use.

The introduction of marihuana use to new groups in countries where its use had been indigenous has resulted in an expansion of scientific interest within many of those countries. In addition to our own direct efforts, we hope to encourage increased research on cannabis use by investigators in other countries. Such research, especially in those countries in which use has been widespread for generations, will do much to increase our understanding of patterns of cultural diffusion and the role of marihuana use within different cultural contexts. If the longitudinal study of users in many countries can be accomplished, it will better assist us in understanding some of the rather contradictory reports of the implications of use. While reports of socially deteriorated functioning related to marihuana use received wide publicity in the past, we have no way of knowing what percentage of users are affected in this way or, indeed, to what extent such deterioration is directly related to cannabis use. As use increases in the United States such knowledge will be valuable in assessing the size of the public health problem that is likely to develop from marihuana use and may enable us to minimize it.

There are a number of important chemical and biomedical research issues that are important in continuing to assess the health implications of marihuana use in the United States. One technical problem is that of developing relatively uniform methods of analysis of cannabis so that the results of one laboratory's assay can be accurately compared to that of another. This is especially important when comparisons are being made between results obtained in the United States and in other countries. At present a collaborative program is underway in which ten analytical laboratories doing cannabis assays are reporting their findings on standard cannabis samples to the National Institute of Mental Health. By evaluating the variations in findings and methodology, we can expect to develop more valid and reliable measures that will facilitate comparisons.

The development of a simple, easily carried out test for marihuana use and intoxication has not yet been achieved. Such a test would be invaluable in determining the extent of marihuana intoxication for both clinical and research purposes. Work is continuing on this problem, and it is hoped that such a test can be developed this year.

Continuing studies of the various products formed during the metabolism of marihuana in the body and of the process by which the drug acts are important to our understanding of marihuana's health implications. This area of study is likely to assist us in anticipating possible drug interactions that may occur as marihuana is used in conjunction with other drugs widely available in our society. Systematic pharmacokinetic studies are needed to better define absorption in the various organ systems of the body and the excretion process. As has been suggested in other sections of this report, the interaction of marihuana with such drugs as alcohol, nicotine, caffeine, barbiturates and stimulants is of particular importance. Such studies have been begun and will continue.

There is evidence in animals that regulation of body temperature may be disturbed by marihuana. Possible effects of exposure to cold while under the influence of marihuana should be examined as well as its role when used in association with febrile illnesses.

Possible toxic effects of cannabis on specific organ systems should continue to be examined with care. Increasing reports of respiratory difficulties associated with heavy smoking of cannabis and the possible effects of marihuana smoking on lung tissue require especially careful examination.

Because clinical reports of adverse effects typically cannot distinguish the role of marihuana from that of other drugs or other aspects of life style, it continues to be important to follow-up these reports by more systematic animal and human studies.

A variety of preclinical animal research data has been accumulated which also requires systematic study in humans. In the past the maximum length of studies of systematic administration in man has been limited to thirty days. As a result of recently completed toxicity studies, it will be possible to extend this period which will permit systematic study of the effects of clearly defined doses of marihuana and its principal psychoactive ingredient, Delta-9-Tetrahydrocannabinol, over more lengthy periods of use. Such studies should include a wide range of areas of psychological and physiological functioning.

The possibility of developing a marihuana antagonist - that is, a drug that will block or reverse the action of marihuana - is worth pursuing. Such a drug may be of value in treating cases of acute intoxication and preventing chronic intoxication.

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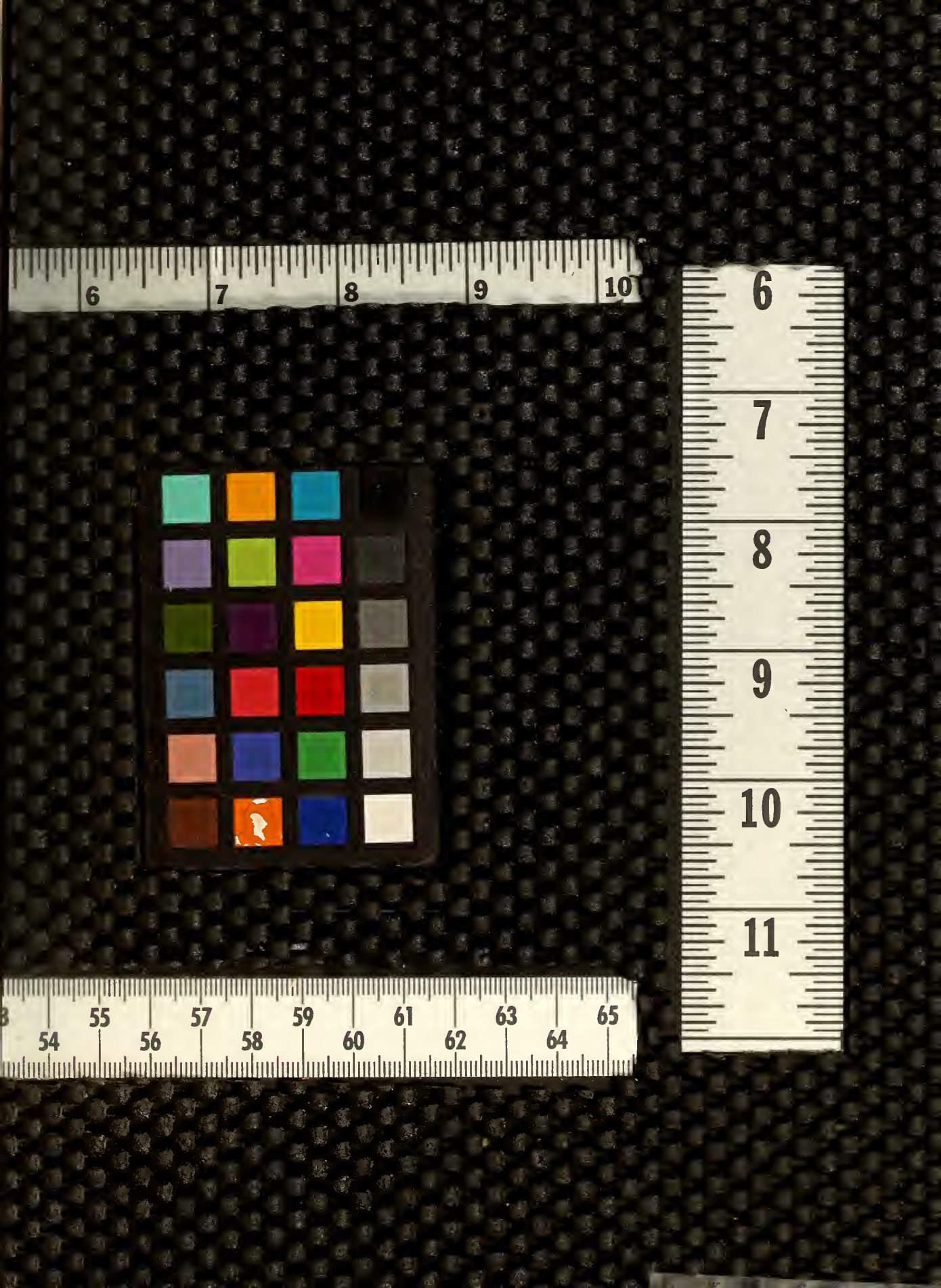
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